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SUPPLEMENTUM 326

JOHN-ERIK JOHNSON

HYSTEROGRAPHY AND
DIAGNOSTIC CURETTAGE
IN CARCINOMA OF THE
UTERINE BODY

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ACTA RADIOLOGICA SUPPLEMENTUM 326

JOHN-ERIK JOHNSON

HYSTEROGRAPHY AND DIAGNOSTIC CURETTAGE
IN CARCINOMA OF THE UTERINE BODY

An evaluation of diagnostic value and therapeutic
implications in stages I and II

STOCKHOLM 1973

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INTRODUCTION

About one fourth of all malignant tumours of the female genital tract originate in the uterine body (Cancer incidence in Sweden 1966). The knowledge whether and to what extent also the cervix is affected facilitates adequate treatment and prognostication of carcinoma of the uterine body. Diagnosis of the lesion and assessment of tumour extension in the corpus and cervix are usually made by diagnostic curettage. Another less widely used method is hystero-graphy. The most likely reason why hystero-graphy is less popular as a diagnostic tool is the possibility of spread of the tumour via the tubes and the vascular system. In addition, the method is thought to carry a risk of dissemination of infectious material from the uterus into the tubes and abdominal cavity.

Diagnostic curettage also implies these risks which are, however, difficult to assess because curettage is regularly the first diagnostic step in the investigation of possible carcinoma of the uterine body.

The first purpose of the present investigation was to assess the value of hystero-graphy and diagnostic curettage for determining the local tumour spread in the uterine body and cervix.

The second purpose was to estimate the risk of dissemination of infectious and malignant material by hystero-graphy and curettage in association with intra-cavitary radium treatment.

The effect of radiation therapy on the primary tumour and its tendency to spread to regional lymph nodes is considered to vary with the extent and degree of histologic differentiation of the tumour.

The third purpose was therefore to find out whether the frequency of residual carcinoma and recurrences in the uterus as well as the frequency of pelvic metastases varies with the local spread and histologic grade of the tumour in such a way as to be useful in the planning of treatment.

The term 'metastases in the pelvic nodes' is used to design those changes detected at lymphadenectomy. When such metastases were discovered at gynecologic examination, the term 'metastases on the pelvic walls' was used instead.

As a rule, the hypotheses were tested by the χ^2 test. Assuming the null hypotheses to be true, the material was considered large enough for statistical evaluation only if the theoretical value was larger than 5. In comparison between groups the probability of random occurrence was designated P. $p > 0.05$ was regarded as not significant.

CHAPTER I

REVIEW OF LITERATURE

Diagnosis and estimation of extent of carcinoma of the uterine body

Hysterography was originally introduced by HEUSSER in 1925 as a method to demonstrate early pregnancy and to investigate sterility. It was later also used in the investigation of carcinoma of the uterine body. After some controversy regarding its value (NIELSEN 1938, SCHULTZE 1939, TASCH 1941, ROBINS 1947 and YURUKOW 1964) it was gradually realised that the method could not only give information regarding the presence of uterine tumour (BECLÈRE 1936, DALSACE & AKNIN 1937, NORMAN 1950, 1969, RUBIN 1955 and ERBSLÖH 1965), but also the local spread of growth including cervical involvement (ROBINS 1947, SIMARD & FORTIER 1948, NORMAN 1950, RUBIN 1955, MERGER, BOUCCARA & BEJAT-SAGLIER 1962, ERBSLÖH 1963, 1965 and YURUKOW 1964, ZSOLNAI & NYIRÖ 1968).

Curettage. Diagnostic curettage has long been the method most widely used for diagnosing malignant tumours of the uterus (RUGE & VEIT 1881). According to CROSSEN (1937), HEYMAN (1941) and GUSBERG (1960), fractional curettage is a useful method for charting the local spread of carcinoma of the uterine body and cervix.

The method generally used is essentially that devised by HEYMAN (1949), described as follows

1. Curettage with a small curet of the lower cervix immediately above and surrounding the external os and prior to the introduction of any other instrument.
2. Curettage of the upper cervix without passing the internal os.
3. Measuring the length of the uterine cavity by passing a sound.
4. Careful dilatation of the cervix without touching the top area of the cavity.
5. Examination of the top area with a uterus canal forceps.
6. Curettage of the corpus immediately above the internal os.
7. Curettage of the corpus and examining of the cavity with the same type of forceps.

The specimens removed from the different part of the cavity should be kept separate and should be microscopically examined separately. When exploring the uterine canal with the sound, the curet and the forceps, irregularities of the cavity and of its wall are often noticeable, offering valuable information as to the site and extent of the lesion.⁴

Many authors do not give a definition of the internal os. They probably mean the os internum anatomicum, also called the os internum canalis isthmi, i.e. the frequently recognised junction between corpus uteri and isthmus uteri.

The os internum canalis cervicis or os externum canalis isthmi, which marks the junction between the isthmus and the cervix is, as a rule, not so readily recognised with the naked eye, but is easier to define histologically (os internum histologicum) RAUBER & KOPSCH 1939, MARTIUS 1950, BRODY 1970).

KOTTMEIER (1959) stressed that with this technique it is possible to demonstrate whether the cervix is involved, though not always with certainty. LEISSNER (1950), and later HELD (1969), however, stressed that even careful fractional curettage can miss malignant tissue, especially in the cervix.

ROBERTS (1960) and WINTERTON (1964) considered curettage to be unreliable for demonstrating cervical involvement because of the risk of contamination of the cervix with tumour fragments from the uterine body.

Technical details under 5. are omitted here.

Complications

Infections

Hysterography. The frequency of complicating salpingitis in the hystero-graphic investigation of sterility has been reported as less than 0.5 % (SCHULTZE 1939). In the investigation of bleeding disorders and pain, the frequency of salpingitis is somewhat higher, viz. 1—2 % (KJELLBERG 1942). Apparently hystero-graphy carries just a small risk of infectious dissemination. The choice of contrast medium (oil- or watersoluble) is less important in this respect (KJELLBERG 1942). Some series of women with carcinoma of the uterine body examined by hystero-graphy have been published. No serious infectious complications (salpingitis) were reported (NORMAN 1950, DAVIDS 1953, GRAZIANI & CATURANI 1961, YURUKOW 1964). The series have, however, been relatively small.

Curettage. Diagnostic curettage is also sometimes followed by infectious complications. The frequency is the same as, or somewhat higher than, that attending hystero-graphy. BOBECK (1952) reported complicating salpingitis in

1 % of 5 543 curettages; ABOLINS (1969) in 6 % of 1 500; and JONASSEN & TÖRNQVIST (1971), in 1.4 % of 843.

In the first 2 series the frequency of salpingitis (1.3 % and 9 %) was higher in out-patients. In the series of JONASSEN & TÖRNQVIST all the operations were ambulatory.

Spread of tumour

Hysterography. One of the main arguments against hysterography in investigation of carcinoma of the uterine body is the alleged risk of spread of the tumour either via the tubes or via the vessels. Some authors regard the risk of tumour dissemination as small or only theoretical (CLASON 1937, ROBINS 1947, NORMAN 1950, GRAZIANI & CATURANI 1961, YURUKOW 1964, TARLOWSKA et coll. 1970). Others adopt a more cautious attitude and warn against the use of hysterography except in selected cases. But they stress at the same time that it remains to be proved whether hysterography involves any risk in this respect (PILLMORE 1946, KOTTMEIER 1959).

Some authors are definitely critical and regard the method as contraindicated because of the alleged risk of spread of the tumour (CROSSEN 1937, TASCH 1941, MACKENZIE 1953, STUDDIFORD 1953).

Most authors, especially of more recent publications, feel, however, that the method is not contraindicated in the investigation of malignant uterine tumours.

Curettage has also been regarded as involving a risk of dissemination of tumour cells via the tubes and the vascular systems (SAMPSON 1934, MILLER 1959). HENRIKSEN (1960) pointed out the need of extreme caution at curettage. WALL et coll. (1967) claimed that diagnostic curettage with a small curet is less traumatic than fractional curettage with dilatation of the cervix, and thus probably causes less spread of tumour cells. This opinion was shared by DIDDLE (1967).

Residual tumour and recurrences in the uterus

The frequency of residual tumour in the uterus after preoperative radiation therapy varies with the technique used. In series in which intracavitary treatment was given and only a cylindrical intrauterine applicator (tandem) was used, the frequency of residual tumour ranged from 20 % to 75 % (Table 1). The frequency thus varies widely, but in more recent series it tends to be lower.

The range of variation is wide even when multiple intrauterine applicators are used. In series treated with a uniform technique the frequency has fallen with increasing 'irradiation dose' (Table 2).

Table 1

Reported incidence of residual malignant uterine growth after use of tandem.

Author and type of application	No. of fractions	Dose per fraction	Inter- val irrad. —op. (weeks)	No. of patients		
	Interval in days			total	with resid. malignant growth (%)	
ARNESON et coll. (1948) — Tandem	1	3 000 —* 6 000 mgh	1—6	13	10	(75)
CORSCADEN & TOVELL (1954) — Tandem and trident	1	4 000 mgh	6—8	123	86	(70)
NUGENT & GLEICHERT (1956) — Tandem		3 600 — 4 000 mgh		36	26	(70)
RANDALL & GODDARD (1956) — Tandem	1		6—8	76	51	(65)
SCHMITZ et coll. (1959) — Y-applicator	$\frac{3}{8}$	2 000 mgh	6—8	71	16	(20)
MONTGOMERY et coll. (1960) — Tandem	1	3 600 — 6 000 mgh	6	84	47	(55)
ALLEN & FRALEIGH (1963) — Tandem	1		6	103	66	(65)
CLIMIE & RACHMANINOFF (1965) — Tandem	1	** 4 800 mgh	6—8	107	47	(45)
CARMICHAEL & BEAN (1967) — Tandem	$\frac{2}{7}$	2 400 — 4 800 mgh	0—8	51	32	(65)
DELGLOS & FLETCHER (1969) — Tandem	$\frac{2}{21}$	2 000 — 2 500 mgh	1—8	35	10	(30)
MARCIAL et coll. (1969) — Tandem	1	3 000 rad at a point 2 cm from the center of the linear source	4—8	22	9	(40)
VONGTAMA et coll. (1970) — Tandem 60 % Packing 40 %		5 500 rad 2 cm lateral to the tandem 5 000—6 000 rad at 2 cm depth from the endometrial surface	6	327	92	(30)

* In addition external treatment was given 200 kV irradiation, HVL = 0.5 mm Cu., FSD = 50 cm 4 fields (10 cm × 15 cm) towards the uterus. 400 R × 3—4 to each field.

** In addition external treatment was given with 2 MV irradiation, HVL 8 mm Pb, FSD = 100 cm, 4 parallel opposing pelvic portals to a mid pelvis dose of approximately 2 500—3 000 R/8—12 days.

Table 2*Reported incidence of residual malignant uterine growth after use of multiple applicators.*

Author	No. of fractions	Dose per fraction	Interval irrad. — op. (weeks)	No. of patients		
	Interval in days			total	with resid. malignant growth (%)	
HEALY & BROWN (1939)	1	1 200—2 700 mgh	6—10	24	21	(85)
		3 000—3 300 "	6—10	25	18	(70)
		3 400—4 000 "	6—10	20	8	(40)
ARNESON et coll. (1948)	1	3 500—7 000 "**	1—6	19	5	(25)
RANDALL & GODDARD (1956)	1		6—8	132	50	(40)
MONTGOMERY et coll. (1960)	1	5 000—6 000 mgh	6	36	12	(35)
JANISCH et coll. (1970)	2	3 000—4 000 "	36—136	27	5	(20)
	14		**			
SALA & DEL REGATO (1962)	1	6 000 mgh	6	31	9	(30)
TARLOWSKA & SIKOROWA (1962)		3 000 R	< 2—8	28	18	(65)
		3 000—5 000 R		59	25	(40)
		5 000—7 000 R		38	10	(25)
		about the external surface of the uterine wall				
CARMICHEAL & BEAN (1967)	2	1 000—2 000 mgh	0—8	142	75	(55)
	21—28					
DELCLOS & FLETCHER (1969)	2	2 000—2 500 mgh	1—8	107	22	(20)
	21					
KJELLGREN & MAGNUSSON (1970)	3	1 000 rad at a distance of 1.5 cm from the nearest radium source	6—12	189	15	(8)
	14					
KELLER et coll. (1971)	1(2) (21)	1 152—6 144 mgh	6	161	53	(35)

* In addition external treatment was given with 200 kV irradiation, HVL = 0.5 mm Cu, FSD = 50 cm. 4 fields (10 cm × 15 cm) towards the uterus. 400 R × 3—4 to each field.

** 'Second look curettage'.

The frequency also varies with the interval between preoperative radiation therapy and operation. This interval often varies in one and the same series. The variation of the pathologists' opinions about the concept 'residual carcinoma' must also be considered.

Some authors have published the frequency of residual carcinoma after preoperative external radiation therapy. Thus, SALA & DEL REGATO (1962) reported residual carcinoma in 70 % of 68 patients treated with 4 000 rad in the uterus (250 kV, HVL 3 mm Cu, SSD 80 cm, four pelvic fields for 6—8 weeks). LAMPE (1963) gave 70 % of patients with residual carcinoma of 121 treated with 4 000 R (200—250 kV, HVL 1—2.7 mm. Cu, four pelvic fields, 15 cm $\times$ 12 cm for 3.5—4 weeks). VONGTAMA et coll. (1970) found residual carcinoma in 5 of 13 patients treated with 4 000—5 000 rad tumour dose to the entire pelvis with 2 MV roentgen irradiation for 4—5 weeks. In the above series the interval between the end of preoperative treatment and surgery was 6 weeks.

The variation in the frequency of residual tumour with local spread of the disease was elucidated by MARCIAL et coll. (1969), who reported residual growth in 19 of 20 cases in stage I (tumour confined to uterine body) and in 4 out of 7 cases of stage II (tumour involving also the cervix).

On the basis of histologic examination of surgical specimens (hystero-salpingo-oophorectomy or at curettage in inoperable cases) KJELLGREN & MAGNUSSON (1970) found residual carcinoma in 5 % of 158 patients in stage I and in 19 % of 31 in stage II.

The frequency of residual carcinoma after preoperative radiation therapy has been claimed to vary to some extent with the histologic grade of the tumour.

TARLOWSKA & SIKOROWA (1962) reported 'undestroyed cancer' after preoperative radiation therapy in 4 out of 9 cases of well differentiated adenocarcinoma. The corresponding values for moderately and poorly differentiated cases of adenocarcinoma were 33 out of 68 and 10 out of 32, respectively.

ARNESON (1964) found remaining tumour in 4 out of 32 patients with well differentiated adenocarcinoma. The corresponding figures for moderately differentiated and for anaplastic carcinoma were 7 out of 14 and 2 out of 4, respectively. CLIMIE & RACHMANINOFF (1965) reported residual growth in the uterus in 19 out of 57 patients with well differentiated tumours, in 10 out of 24 with moderately differentiated growths, and in 14 out of 18 with poorly differentiated adenocarcinoma, respectively.

In contrast with the above mentioned authors, RANDALL & GODDARD (1956), found the frequency of residual growth in a series of 208 patients not to vary with the histologic grade of the tumour.

DELCLOS & FLETCHER (1969) found recurrences in 6 out of 51 cases treated only with the packing method and in 2 out of 5 treated with a tandem.

JANISCH et coll. (1970) found carcinoma in 5 out of 27 cases at 'second look curettage' 9—34 months after intracavitary radium treatment. Multiple sources were used (^{60}Co pearls). KOTTMEIER (1954) found recurrences in 15 % of 990 cases of carcinoma of the uterine body and in 12 % of 204 cases of carcinoma of the corpus and endocervix (tumour involving the body and the cervix regardless of any tumour extension outside the uterus. The definition was given according to the Annual report on the results of radiotherapy in cancer of the uterine cervix, fifth volume, HEYMAN 1949).

KARLSTEDT (1968) reported a recurrence of the carcinoma in the uterus in 11 % of 864 patients in stage I and in 13 % of 103 in stage II.

In the last two series the patients were treated primarily with radiation therapy only (HEYMAN's packing method) and the frequencies were based on findings at operations performed because of possible recurrence.

Metastases on pelvic walls

Carcinoma of the uterine body is often confined to the primary organ for a long time. According to WAY (1951), spread via the lymphatics is rare except in very advanced cases and in patients with anaplastic tumours. KOTTMEIER (1954) also felt that metastases in the pelvic lymph nodes were rare (in 3.3 % of 1 267 patients) when the original tumour was otherwise confined to the uterine body. WILLMOTT DOBBIE et coll. (1965) gave a similar frequency (in 3.5 % of 730 patients) and BORONOW (1969) gave an even lower frequency. When the tumour was confined to the uterine body, no metastases were found in the pelvic lymph nodes in any of 71 patients, while 1 of 24 patients had such metastases in cervical involvement (stage II).

RICKFORD (1968) found metastases in the pelvic lymph nodes in about 10 % : in 2 out of 36 patients when the tumour was confined to the uterine body and in 2 out of 9 with also cervical involvement. DELCLOS & FLETCHER (1969) reported 7 % out of 138 and 18 % out of 50, respectively.

The view that spread to the pelvic lymph node groups is rare or relatively rare has been challenged by, among others, JAVERT & HOFAMMANN (1952), LIU & MEIGS (1955), SCHWARTZ & BRUNSCHWIG (1957), HAWKSWORTH (1959), ROBERTS (1960), DAVIS (1964) and LEES (1969) who reported metastases in the pelvic lymph nodes in 14—48 %.

The results were obtained at lymphadenectomy at hysterectomy. The series were relatively small and selected which presumably explains the high frequency of metastases.

Most investigators found the frequency of metastases to be higher when the

tumour had grown juxtacervically or down into the cervix or when the tumour had infiltrated the myometrium (LIU & MEIGS 1955, LEFÈVRE 1956, SCHWARTZ & BRUNDSCHWIG 1957, CARMICHAEL & BEAN 1967 and GRÜNBERGER 1968).

The tendency of a tumour to spread to the regional lymph nodes also appears to vary with the histologic grade of the tumour (RANDALL & GODDARD 1956, BOUTSELIS et coll. 1963). WILMOTT DOBBIE et coll. (1965) reported undifferentiated or anaplastic tumour in 17 out of 20 patients with metastases in the lymph nodes. Of the entire material (291 patients), 41 % had undifferentiated or anaplastic carcinoma.

LEES (1969) found poor differentiation in 5 of 13 cases with lymph node metastases compared with 11 out of 63 without lymph node metastases.

CHAPTER II

MATERIAL AND METHODS

During the 1951—1960 period 902 patients were admitted to the department, because of carcinoma of the uterine body. Of these patients, 6 were not offered treatment because of high age or poor general condition. Three patients refused treatment. This left 893 patients for the present investigation (Fig. 1).

The receiving area of the department covers the most southern part of Sweden (with the exception of the city of Malmö), including about 1.2—1.5 million inhabitants. Assessment of the extent of the tumour was based on fractional curettage in accordance with recommendations given by HEYMAN 1949. The patients were classified according to KOTTMEIER 1964 (Annual report ...) as follows

‘Stage 0

Histologic findings suspicious of malignancy but not proven.

Stage I

The carcinoma is confined to the corpus.

Stage II

The carcinoma has involved the corpus and the cervix.

Stage III

The carcinoma has extended outside the uterus but not outside the true pelvis.

Stage IV

The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum.’

When the surgeon reported that the operation included fractional curettage, the disease was staged on the basis of the results of the primary curettage. When not treated in this way, cervical or fractional curettage was done at the time of the first radium treatment. The junction between the corpus and the cervix was defined as the internal os (os internum anatomicum — os internum canalis isthmi (see page 7).

The disease was classified as stage 0 in 23 patients, as stage I + II in 811, as stage III in 49 and as stage IV in 10. 42 patients with carcinoma stage I + II had been primarily operated upon at other hospitals and received only post-operative radiation therapy (Fig. 1).

Carcinoma of
uterine body

893

Stage 0	Stage I + II	Stage III	Stage IV
23	811	49	10

Primary irradiation	Primary surgery	Primary surgery at other hospitals + postop. irradiation at the department	Incomplete hospital records
764	3	42	2

Examined with hystero-graphy		Not examined with hystero-graphy	
606		158	
Stage I	Stage II	Stage I	Stage II
516	90	130	28

Hystero-graphs after examination; carcinoma demonstrable; examination technically satisfactory		Hystero-graphs untraceable		No carcinoma demonstrable		Technically unsatisfactory	
578		10		14		4	
Stage I	Stage II	Stage I	Stage II	Stage I	Stage II	Stage I	Stage II
490	88	9	1	14	0	3	1

Fig. 1. Carcinoma of the uterine body 1951—1960.

769 patients with carcinoma stage I + II were primarily treated at the department. In 2 cases the hospital records were incomplete, and 3 patients were operated upon primarily, leaving 764 patients for further analysis.

Hysterography

From 1947 most of the patients with carcinoma of the uterine body were examined with hysterography. This was performed 2—5 weeks after primary curettage. The technique and interpretation of the findings have been described in detail by NORMAN (1950, 1956).

The instrument designed by SCHULTZE was used though with cones of various sizes to permit the choice of one that fitted snugly into the cervix. The nozzle of the cannula should project only a few millimeters beyond the cone, this being necessary not only to minimise the risk of perforation, but also to allow demonstration of any changes in the cervix.

Water soluble contrast media were used: before 1957 Umbradil-Viscous H (Astra) and after that year, Perjodal-H-viscous (Pharmacia). The examination was carried out under fluoroscopic control. This enabled the examiner to follow the passage of the contrast medium into uterine cavity and to expose films with optimal filling in necessary positions.

The hysterograms included in the present investigation were re-examined with respect to the following details:

1. Extent of tumour of uterus
 - A. Confined to uterine body
 - B. Involvement also of upper third of cervix
 - C. Involvement also of upper two thirds of cervix
 - D. Involvement also of more than upper two thirds of cervix
2. Flow of contrast medium into at least one of the tubes
3. Vascular backflow of contrast medium

The internal os was taken as the borderline between the uterine body and the cervix.

Principles of treatment

Intracavitary radium treatment according to the packing method of HEYMAN (1941) was used. In cases examined with hysterography treatment was given the day after the examination. As a rule, a second treatment was given 3—4 weeks after the first. Hysterography was usually performed also the day before the second treatment. In some cases treatment was given again 3 weeks later. In some cases healing after the end of radiation therapy was checked hysterographically.

The intracavitary radium treatment was sometimes supplemented by external irradiation. The principles of treatment were the same in the entire material and are described on page 19. The technique used does not allow calculation of absorbed doses delivered in the individual cases (page 57). Thus, it was not possible to classify the material in this respect.

When possible hystero-salpingo-oophorectomy was performed 1–3 months after the end of irradiation.

Recurrences or metastases in the ovaries of patients primarily given only radiation therapy were treated surgically unless contraindicated by the patient's general condition.

The diagnosis of recurrences and metastases was made by physical and roentgenographic examinations. In some cases needle aspiration, curettage or biopsy was done. The surgical specimens were all examined at the Institute of Pathology, Lund.

Cases treated primarily with radiation therapy only were not grouped according to progression of residual tumour or recurrences (FINN 1950).

The mortality from the tumour (for details see KARLSTEDT 1968), recurrences and metastases was calculated from a follow-up period of 5–14 years.

All the patients were regularly controlled at the department according to the principles described by LINDGREN (1962).

Patients examined with curettage and hystero-graphy

606 (79 %) patients were examined with hystero-graphy (Fig. 1). 450 (74 %) of these were examined more than once. Ten hystero-graphs could not be traced for repeat viewing. In 14 patients the tumour could not be demonstrated roentgenologically. Four examinations were interrupted owing to technical mishaps. The age distribution is given in Table 15. 175 (29 %) were nulliparous.

In 604 patients the size of the uterus was estimated with a sound (Table 3). 279 (46 %) of the patients received only radiation therapy, while 327 (54 %) received both radiation therapy and surgery.

In 516 (85 %) patients the growth was found to be in stage I, and in 90 (15 %) in stage II.

In 578 patients the local spread of the tumour could be assessed both from hystero-graphs and from histologic examination of the curettings. A correlation, if any, of residual tumour, recurrences, and metastases with the local spread of the tumour in the uterine body and cervix was studied separately in this group.

Capsules of two sizes (ϕ 4 mm $\times$ 20 mm and ϕ 8 mm $\times$ 20 mm) were used for intracavitary radium treatment. Each applicator (capsule) contained

Table 3

Size of uterus as measured with probe in 604 patients examined with hystero-graphy.

Length in cm	No. of patients	Per cent
6	22	3.7
7	130	21.5
8	190	31.5
9	122	20.2
10—11	106	17.5
≥ 12	34	5.6
Total	604	100.0

Table 4

Number of intrauterine treatments given to 578 patients.

No. of treatments	No. of patients
1	77
2	497
3	4
Total	578

Table 5

Time of operation.

Months after end of radiation therapy	No. of patients
1	101
1—3	160
4—5	29
6—7	8
8—9	3
10—12	4
Incomplete hospital records	6
Total	311

10 mCi ^{226}Ra . Active length was 8 mm. The absorbed dose 2 mm from surface of the respective applicators and measured in a plane perpendicular to their longitudinal axis through the middle of the active part was 370 rad/h and 160 rad/h, respectively. If small uterus, a tandem was used instead (ϕ 7 mm $\times$ 68 mm, 90 mCi ^{226}Ra). Absorbed dose 15 mm from surface of the applicator was 200 rad/h. A tandem was used on 84 occasions. As a rule, 2 intrauterine treatments were given at an interval of 3 weeks (Table 4).

The number of intrauterine capsules used varied between 5 and 30. At each treatment 1 120 mCih (5 capsules) — 2 720 mCih (30 capsules) were given according to the number of capsules. When the capsules had a diameter of 8 mm the duration of treatment was increased by about 20 %. When a tandem was used, 1 800 mCih was given.

Patients with stage I lesions received one vaginal treatment and no external radiation, those with stage II lesions two vaginal treatments and external treatment.

Vaginal applicators, either in the form of a cylinder filling the entire vagina or a flat applicator placed against the portio or along the vaginal cavity were used on one or two occasions. 'Doses' of 1 000—1 900 and 2 000—3 600 mCih, respectively, were given.

Patients receiving also external irradiation were given 1 000—2 000 R to 2 lower abdominal fields and 2 lower dorsal fields, with the beam directed towards the parametria and the pelvic wall (180 kV, HVL 1 mm Cu, FSD 60 cm). Field size was 150—200 cm². 500 R was delivered to one field per day. The abdominal fields were regularly irradiated at the time of the first intracavitary treatment, while the dorsal fields were irradiated at the second treatment 3—4 weeks later. In 311 patients in whom treatment included surgery the operation was performed 1—12 months after the end of radiation therapy (Table 5). The preoperative intracavitary treatment given is summarised in Table 6. 35 of 266 patients with stage I and 33 of 45 with stage II lesions received external roentgen treatment preoperatively.

Three patients were subjected to surgical exploration, 4 to subtotal hysterectomy, and the remaining 304 to hysterectomy. Because of probable lymph node metastases, the lateral external iliac and interiliac lymph nodes were removed in 4 patients at hysterectomy (GORTON 1953, REIFFENSTUHL 1964) (Table 7.) No further radiation treatment was given if the histologic examination showed no residual tumour or tumour in the endometrium only.

The other patients received postoperative roentgen treatment (180 kV, H.V.L. 1 mm Cu, FSD 60 cm) 1 500—2 000 R to a lower abdominal field and in some cases also to a lower dorsal field. Field surface about 300 cm². The central beam was directed 15° caudally (fractionation see page 19).

Table 6*Intracavitary preoperative radium treatment of 311 patients.*

No. of intrauterine treatments	No. of patients		
	Stage I	Stage II	Total
1	60	13	73
2	205	32	237
3	1		1
Total	266	45	311
No. of intravaginal treatments			
0	54	8	62
1	191	13	204
2	21	24	45
Total	266	45	311

Table 7*Type of operation in patients with stage I and II carcinoma.*

	No. of patients
Explorative laparotomy	3
Subtotal hysterectomy + salpingo-oophorectomy	4
Total abdominal hysterectomy + salpingo-oophorectomy	292
Total vaginal hysterectomy + salpingo-oophorectomy	8
Total abdominal hysterectomy + salpingo-oophorectomy + excision of pelvic lymph nodes	4
Total	311

267 patients were given only radiation therapy. The principles of intracavitary treatment are given in Table 8. 31 of 224 patients with stage I carcinoma and 21 of 43 with stage II were given external roentgen treatment.

Recurrences or metastases were suggested or demonstrated in 105 patients after radiation therapy. Of these patients, 64 were operated upon (Table 9). In 19 of the operated cases no malignant tissue could be demonstrated at operation or at histologic examination of the surgical specimens.

Table 8*Intracavitary radium treatment of 267 patients.*

	No. of patients		
	Stage I	Stage II	Total
No. of intrauterine treatments			
1	2	2	4
2	220	40	260
3	2	1	3
Total	224	43	267
No. of intravaginal treatments			
0	5	0	5
1	187	12	199
2	32	31	63
Total	224	43	267

Table 9*Recurrences or metastases. Type of operation*

	No. of patients
Explorative laparotomy	5
Subtotal hysterectomy + salpingo-oophorectomy	3
Total abdominal hysterectomy + salpingo-oophorectomy	54
Total vaginal hysterectomy + salpingo-oophorectomy	1
Oophorectomy	1
Total	64

Patients examined with curettage only

Because of prevailing anatomic conditions in the vagina, high age, or technical reasons 158 (21 %) patients were not examined with hystero-graphy. The age distribution is given in Table 15. 83 (53 %) were nulliparous. The size of the uterus was estimated with a sound and recorded in 155 patients (Table 10). 92 (58 %) of the patients received only radiation therapy while 66 (42 %) were treated with both irradiation and surgery.

130 (82 %) had stage I carcinoma and 28 (18 %) had stage II.

Table 10

Size of uterus as measured with probe in 155 patients not examined with hystero-graphy

Length in cm	No. of patients	Per cent
6	7	5
7	25	16
8	47	30
9	34	22
10—11	31	20
≥ 12	11	7
Total	155	100

Microscopic examination

Histologic grading. On admission of a patient to the department the original slides of the primary diagnostic curettings were always re-examined at the Institute of Pathology and used for histologic grading.

Slides from 711 (93 %) of 764 patients were examined (53 preparations were missing). In 3 the microscopy showed carcinosarcoma. 708 patients had adenocarcinoma and these were analysed further.

The degree of differentiation of the tumours was assessed according to the criteria given by KARLSTEDT (1968) as follows Grade 1. Highly differentiated carcinoma. 'The tumours in this group are well organised, and either papillary or adenomatous. In the former, papillary cords may be covered with a single layer or a few layers of uniform cells, with little, if any, polymorphism. In some papillary tumours the epithelium may tend to form an irregular pattern similar to that found in mesonephric tumours of the ovary. Adenomatous tumours are distinguished by slight irregular structures, often tightly packed, with a minimum of stroma; they are synonymous with 'adenoma malignum'. The epithelium differs little from that of normal mucosa in the proliferative phase of the menstrual cycle, and there is negligible anaplasia. To this group are also assigned adenomatous carcinomas where the epithelium resembles the glandular structure of the normal mucosa in the secretory phase of the menstrual cycle. Minute solid areas may be found, sometimes with squamous differentiation. These are as highly differentiated as the rest of the tumour, and only slight anaplasia may be encountered.'

Grade 2. Moderately differentiated carcinoma. 'The tumours are adenomatous and less well organised than those in the previous grades, and solid areas

Table 11

Histologic grading versus stage I and II. Figures in brackets denote corresponding figures in Karlstedt's publication

	Histologic grade			
	1	2	3	4
Stage I	332 56 % (9 %)	189 32 % (72 %)	50 9 % (12 %)	20 3 % (7 %)
Stage II	48 41 % (0 %)	41 35 % (50 %)	17 15 % (33 %)	11 9 % (17 %)

are common. The epithelial proliferations are irregular, and the individual cells are devoid of polarity. There is obvious polymorphism and mitotic figures may be numerous.'

Grade 3. Poorly differentiated carcinoma. 'The carcinoma of this group is predominantly solid, with more or less marked polymorphism and numerous mitotic figures. In most cases, however, there are small areas with identifiable adenomatous structures. Squamous differentiation may sometimes be present though diffuse, with little if any sign of keratinisation. Because of the solid nature of these tumours they may occasionally be difficult to identify as true adenocarcinomas.'

Grade 4. Anaplastic, undifferentiated carcinoma. 'The structure is entirely undifferentiated. In some, the growth consists of solid anaplastic cords of immature cells, with no sign of adenomatous differentiation. In others the cord merge to form a diffuse proliferation which may display marked polymorphism reminiscent of a sarcoma.' No search was made of any differentiation of squamous epithelium in the tumours.

The results of grading in the present material deviated markedly from those of KARLSTEDT (Table 11).

For the morphologist the reasons are obvious. The grading of a tumour is in several respects subjective. The grading may be less uniform because some examiners attach more importance to the histologic findings than to the cytologic picture.

In stage I half of the cases were classified as grade 1, one third as grade 2, and the rest as grade 3 + 4. In stage II grade 3 + 4 was twice as common as in stage I.

Table 12
Prognosis versus histologic grade in stage I

Died from tumour (observation period 5—14 years)		'Crude 5-year deaths' Karlstedt's material
Grade	Present material	
1	14 %	10 %
2	16 %	27 %
3+4	40 %	43 %

The most striking feature was the low frequency of grade I in KARLSTEDT'S material, which was very marked in stage II (0 %). In both materials, however, the grade tended to be higher in stage II, especially in KARLSTEDT'S material (50 % of the patients in stage II had been assigned to grade 3 + 4).

A factor usually correlated with the degree of differentiation is the prognosis (Table 12). In both materials the patients with a higher grade had a poorer prognosis, but, according to KARLSTEDT, the prognosis varied more closely with the histologic grade. The distinct trend in the present material suggests that the results could be used in the further analysis.

The difference in distribution of histologic grading might be explained by morphologic differences. The clinical material in both investigations are reasonably uniform and comparable with a similar distribution of the various stages. It thus appears clear that the differences are due mainly to differences in the histologic interpretation.

Microscopy and staging

The histologic findings are of decisive importance for differentiation between stages I and II (KOTTMEIER 1964). The interpretation of the histologic material, especially the findings in the cervical portion as well as the procedures for the technical processing of the frequently scanty cervical material is thus of utmost importance.

Patients in stage I examined with hystero-graphy were selected. The primary curettings obtained with the fractional technique as well as the curettings obtained at the first radium treatment (secondary curettings) were re-examined microscopically.

At the primary examination only one slide prepared from the cervical scrapings was examined. From the paraffin blocks 3—4 new slides were processed in 'step sections' in cases which did not contain malignant tissue at the re-examination.

Table 13*Diagnosis from cervical curettings from 104 patients originally classified as stage I*

	Primary curettings	Secondary curettings
Carcinoma at primary examination	14	14
Carcinoma at re-examination of original slides	1	1
Carcinoma after step sections of cervical curettings	2	10
No carcinoma	10	52
Total	27	77

(Serial section means consecutive sectioning of the paraffin block with a subsequently large number of slides. Step section means a modification, where the blocks is cut into considerably less numerous sections with interruptions and consequently a smaller number of slides.) Cervical curettings from 104 cases were available for this re-examination. In 27 of these the material consisted of curettings from primary diagnostic curettage and in 77, of curettings obtained at the department of radiation therapy in association with treatment (Table 13).

In 12 cases the more complete investigation of the curettings revealed at least small tumour fragments. The stage to which a given case is assigned may thus depend on purely technical factors of the histologic examination.

The relation negative to positive findings at re-sectioning the paraffin blocks was about the same in primary and secondary curettings. For further discussion of results, see Chapter III.

Re-examination of operative specimens

It was considered of interest in these cases to compare the results of routine examination of the operative specimens with those obtained at the re-examination. 311 of the patients examined with hystero-graphy had received preoperative radiation therapy followed by operation (see page 20). In 280 of these cases the operative specimens were available for re-examination. The results were discordant with those of the primary examination in 31 (11 %) (Table 14).

In the irradiated tissue it is often difficult to distinguish between radiation induced cell changes and tumour cells. Even isolated groups of endometrial cells in the myometrium sometimes offer difficulties, as they might represent foci of adenomyosis with radiation induced atypia.

Table 14

Histologic findings among 31 patients where the results of the re-examination were discordant with those at the primary examination

Primary examination		Re-examination	
Findings	No. of patients	Findings	No. of patients
No carcinoma	26	Carcinoma of endometrium	12
		Carcinoma of myometrium	13
		Carcinoma of endometrium, myometrium, adnexa and peritoneum	1
Carcinoma of endo- and myometrium	1	Carcinoma of myometrium and adnexa	1
Carcinoma of adnexa	4	Carcinoma of myometrium and adnexa	3
		Carcinoma of myometrium	1

This difficulty is greatest in the evaluation of irradiated well differentiated adenocarcinoma cells in the endometrium. The difference was, however, small and can probably be explained by different opinions of examiners.

Comparison between patients examined and not examined hysterographically

606 patients with carcinoma of the uterine body stage I and II referred to the department were examined with hystero-graphy. Hystero-graphy was not performed in 158 patients. These groups were compared regarding age, parity, weight, size of uterus, stages of carcinoma and frequency of operations (Tables 3, 10, 15).

The patients in the group examined with hystero-graphy were younger than those in the other group. The number of nulliparous women in the group examined with hystero-graphy was smaller. The difference was significant ($p < 0.001$), between the two groups regarding these variables.

The frequency of patients operated upon in the group examined with hystero-graphy was also larger. The difference was significant ($p < 0.01$). The two groups were thus not comparable in these respects which is natural in this non-randomised material.

The distribution of the histologic grading of the tumours examined and not

Table 15*Comparison of age distribution of patients examined and not examined with hystero-graphy*

Age	No. of patients exam. hyst.	No. of patients not exam. hyst.	Total
30—40	6	0	6
41—45	20	4	24
46—50	58	7	65
51—55	117	22	139
56—60	111	27	138
61—65	119	21	140
66—70	79	26	105
71—75	61	22	83
76—80	28	14	42
81—90	7	15	22
Total	606	158	764

Table 16*Histologic grade*

Grade	No. of patients examined with hystero-graphy	No. of patients not examined with hystero-graphy
1	294 (52 %)	86 (59 %)
2	192 (34 %)	38 (26 %)
3	57 (10 %)	10 (7 %)
4	20 (4 %)	11 (8 %)
1—4	563	145

Table 17*Mean age for various patient groups*

	Histologic grade				Examined with hystero-graphy	Not examined with hystero-graphy
	1	2	3	4		
No. of patients	380	230	67	31	563	145
Mean age	59.8	59.8	62.8	62.8	59.3	64.1

examined with hystero-graphy also differed ($p < 0.05$) (Table 16). The difference in age distribution of the two materials may explain the differences in their histologic differentiation (Table 17).

CHAPTER III

RESULTS

Local spread of tumour

The spread of the tumour in the uterine body and cervix was estimated roentgenologically and histologically in 578 patients. Fractional curettage revealed that the tumour was in stage I (confined to the uterine body) in 490 (85 %) and had involved both the body and the cervix in the remaining 88 (15 %). The accuracy with which fractional curettage can map cervical tumour growth was investigated in 104 cases (page 25) in all of which the tumour was classified as stage I. The results are given in Table 18.

In 28 cases the pathologists reported malignant tissue already at the primary microscopic examination. These cases had nevertheless been classified as stage I. This was because of misinterpretation in 5 cases. In the others the malignant fragments were small and regarded as contaminants from the tumour in the uterine body. In 3 of these cases the surgeon had noted in his report that the cervix was open (diam. 7—8 mm) and that it was impossible to decide whether the tissue fragments emanated from the cervix or the corpus. This staging was made in accordance with the recommendations given in the Annual report (HEYMAN 1949) according to which the earlier of two stages should be chosen in doubtful cases.

In 2 cases the cervical carcinoma fragments were missed at primary examination. Step sections from the paraffin blocks revealed malignant tissue in a further 12 cases.

Hysterographically the tumour was confined to the uterine body in 292 (51 %) patients. In 202 (35 %) cases also the upper third of the cervix was involved. The corresponding figures for the upper two thirds were 76 (13 %) and for involvement of more than the upper two thirds 8 (1 %). (Figs 2, 3, 4, 5.) The tumour was, thus, confined to the uterine body in 51 %, but involved also the cervix in the remaining 49 % (Fig. 6). The tumours are grouped according to local spread in Table 19.

The cervical curettings (104) were further examined for any correlation with the hystero-graphic tumour extent. The results are given in Table 20.

Table 18*Diagnosis in cervical curettings from 104 patients originally classified as stage I*

	No. of patients	Per cent
Carcinoma at primary examination	28	27
Carcinoma at re-examination of original slides	2	2
Carcinoma after step sections of cervical curettings	12	12
No carcinoma	62	59
Total	104	100

Table 19*Extent of tumour as judged by hystero-graphy and fractional curettage*

Extent of tumour as judged by		Curettage	
Hystero-graphy		In corpus only (Stage I)	In corpus + cervix (Stage II)
In corpus only	292	288	4
In corpus + upper third of cervix	202	157	45
In corpus + upper two thirds of cervix	76	43	33
In corpus + more than two thirds of cervix	8	2	6
Total	578	490	88

Table 20*Carcinoma fragments in cervical curettings from 104 patients in stage I*

Site of tumour hystero-graphically	No. of patients	No. of patients with malignant tissue in cervical curettings	No. of patients with malignant changes in cervical curettings discovered in step sections
Corpus only	51	15 (~ 29 %)	1/36
Corpus and cervix	53	27 (~ 51 %)	11/38

Comments

Hystero-graphy. The hystero-graphic examination thus demonstrated the presence of tumour in the corpus and cervix in 49 % of the patients.

Careful location of the internal os in the hystero-graph is of decisive importance



Fig. 2. Tumour confined to uterine body.

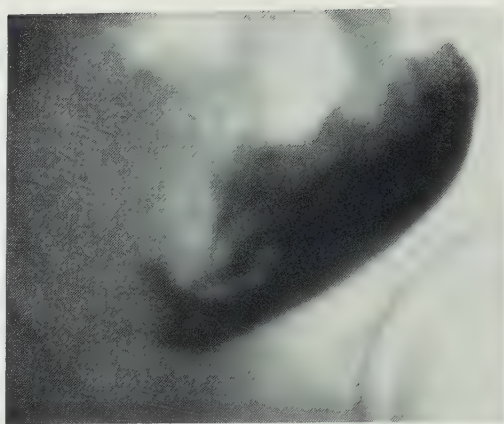


Fig. 3. Tumour involving uterine body and upper third of cervix.

for deciding whether the cervix is the site of malignant growth. The junction between the corpus and cervix, as seen in the hystero-gram, has been described in detail by KJELLBERG (1942), ASPLUND (1952) and FERNSTRÖM & BORELL (1970).

In the early period (1947—1950) of hystero-graphy the isthmus was often regarded as part of the uterine body, but for practical reasons it has gradually been considered as part of the cervix, and the level of the internal os has been used as a border between the uterine body and the cervix (NORMAN). The os internum anatomicum is sometimes fairly easy to recognise in the hystero-gram (Figs 2, 7), but may sometimes be very difficult (Fig. 8). To illustrate this a brief account is given of the site of the internal os in a few typical cases (Figs 2, 7, 8).

The ability of hystero-graphy to demonstrate cervical involvement is not known with any degree of certainty (YURUKOV 1964). ERBSLÖH (1963) reported that this occurs 'quite frequently'. With the criteria now used for determining the level of the internal os the frequency of cervical involvement is 49 %. This figure is close to that (43 %) given by LEISSNER (1950) in an investigation of primarily operated carcinomas of the uterine body. The present investigation shows that hystero-graphy can give detailed information about the extent of a tumour in the corpus and cervix uteri. But the uncertainty in determining the level of the internal os sometimes makes it difficult to state whether a tumour has involved the upper part of the cervix or not.

Curettage. The cervix is alleged to be involved in 8—40 % of all cases of carcinoma of the uterine body. The frequency of cervical tumour growth as estimated from fractional curettage, has been reported as 15—22 per cent in series in which no distinction was made between those in which the tumour was



Fig. 4. Tumour involving uterine body and upper two thirds of cervix.

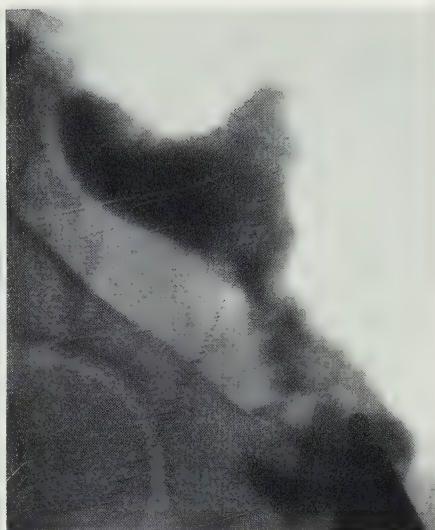


Fig. 5. Tumour involving uterine body and more than upper two thirds of cervix.

confined to the uterus or had spread extra-uterinely (KOTTMEIER 1954, ARNE-SON 1964, THOMPSON & GRAHAM 1964). In one investigation (CARMICHAEL & BEAN 1967) the cervix was found to be involved in only 1 %.

In other reports of patients in stages I + II, carcinoma was demonstrated also in the cervix in 8—11 % (GUSBERG & YANNOPOULOS 1964, ANDERSON *et coll.* 1965, BICKENBACH *et coll.* 1965, KARLSTEDT 1968).

In series examined with fractional curettage, in which the staging was corrected by microscopy of the hysterectomy specimens cervical growth has been found in 12—16 % (RANDALL & GODDARD 1956, ROBERTS 1961).

Cervical involvement, as estimated only from specimens obtained at primary operation, revealed growth in the cervix in 30—43 % (LEISSNER 1950, LIU & MEIGS 1955). JAVERT & HOFAMMANN (1952), reported cervical tumour growth in only 10.7 %. But 19 % of their patients had received preoperative radiation therapy.

The widely variable frequency of cervical involvement can be explained to some extent by differences in the criteria used for selection of the materials, but the method used for demonstrating tumour in the cervix seems to be the most important factor. The lowest frequencies have been found when fractional curettage was used; the highest on the basis of histologic examination of surgical specimens from primarily operated cases.

The value of fractional curettage is thus limited by:

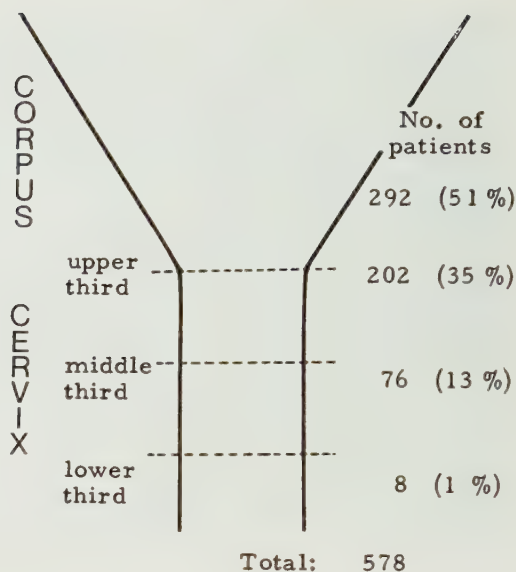


Fig. 6. Hysterographic extent of tumour.

1. difficulties in determining the level of the internal os with the curet.
2. the risk of contamination of the cervical curettings with material from the corpus and
3. the risk that the pathologist will overlook small tumour fragments at the microscopy.

The frequency of cervical involvement in the present series was less certain because primary curettage was often not fractionalised. A repeated curettage may be less informative for mapping the original extent of the tumour as large parts of it may have been removed at the first operation (JOHNSSON & STORMBY 1968). According to HEYMAN (1949), this applies particularly to the cervix. JAVERT & HOFAMMANN (1952) reported complete removal of the tumour by diagnostic curettage in 22 of 51 cases with the lesion confined to the endometrium.

After diagnostic curettage NORDLANDER (1953), CORSCADEN & TOVELL (1954) and LEFÈVRE (1956), SANDBERG & McLENNAN (1957) found no residual tumour in 13 of 133, 2 of 62, 4 of 45, and 3 of 39 cases, respectively. KARLSTEDT (1968) reported 16 out of 276 cases without residual tumour at operation after curettage. This means that in several cases the results of fractional curettage cannot be verified by histologic examination of the extirpated uterus.

Examination of the surgical specimens, however, gives a better picture of the tumour extent even with preceding curettage. This is clear from the investigation by LEISSNER (1950). At examination of 81 women primarily operated upon



Fig. 7. Normal hystero-gram.
Isthmus marked by arrows.

because of carcinoma of the uterine body, 43 % had malignant growth also in the cervix.

The difficulty to ascertain the position of the internal orifice with the curettage and the risk of tumour tissue contamination has been stressed by LEISSNER 1950, ROBERTS 1961, WINTERTON 1964, HELD 1969.

If both isthmus or cervical mucosa and tumour occur in the same tissue sample the engagement of the corpus tumour to the cervix is obvious (KJELLGREN 1967). The finding of only tumour fragments in the cervical scrapings and no other tissue does not, however, prove cervical involvement.

Even when the internal os is located it is technically difficult and often impossible to decide from where in the vicinity of the internal os the tissue fragment has been removed. It is thus only possible to say that the tissue fragments emanated from the region of the internal os without exactness.

Another important detail in the spread of the tumour is the infiltration of underlying tissue. Curettage can occasionally demonstrate such growth (SCHMITZ & SCHMITZ 1935, CROSSEN 1937, GUSBERG 1960, KJELLGREN 1967) but no attempt was made to evaluate this in the present investigation.

The results of step sections of cervical curettings, agreed with the results of other investigations where such a procedure revealed malignancy not found in the primary routine section. Examples are lymph nodes in carcinoma of the uterine cervix (REIFFENSTUHL 1967) or in needle biopsies of the liver (CONN & YENNER 1963, CONN 1972).

It is difficult to judge the importance of the results obtained at re-examination and step sections of cervical curettings. The re-examination could only be carried

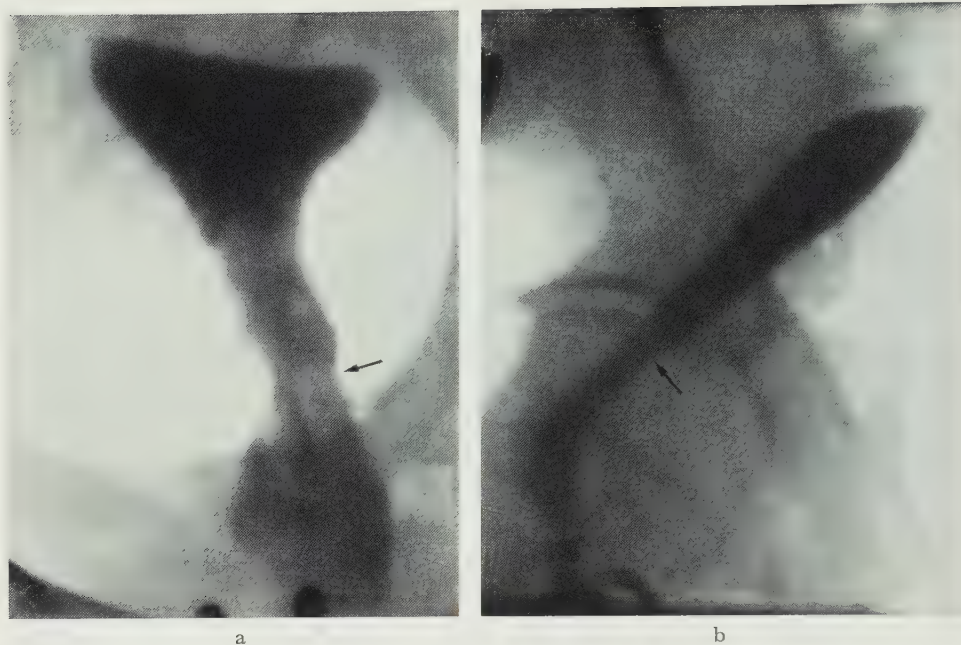


Fig. 8. Triangular uterine cavity with long cervix. The border between corpus and cervix is diffuse. Arrow points to area selected as os internum anatomicum. Hystero-gram 3 weeks after end of first course of intracavitary irradiation. Residual carcinoma in lower part of corpus and large parts of cervix. a) Frontal view. b) Lateral view.

out on a relatively small part of the material and it is thus not possible to say whether it was representative of the material as a whole.

The results do, however, illustrate the drawbacks of fractional curettage. Even if the microscopic examination is performed with utmost scrutiny the most important source of error will still exist, namely the difficulty to recognize if the scraping material originates from the cervix or the uterine body.

Hystero-graphy and curettage. In the present series curettage was used for the primary diagnosis and hystero-graphy was performed 2–5 weeks later. Of the 490 patients where curettage revealed tumour only in the uterine body, hystero-graphy demonstrated growth also in the cervix in 202 (41%). This frequency of involvement in stage I cases agrees with that given by LEISSNER (1950) in his histopathologic examination of surgical specimens.

Curettage revealed tumour extension to the cervix in 88 patients (stage II). In 4 of these where hystero-graphy failed to prove cervical involvement, recurettage revealed tumour left in the cervix as well as in corpus in 3 patients and no signs of malignancy in one.

Table 21*Frequency of flow of contrast medium into tubes or vascular backflow among 592 patients*

Extrauterine flow	No. of patients	Per cent
Into tubes only	311	53
Vascular backflow only	50	8
Into tubes + vascular backflow	123	21
None	108	18
Total	592	100

Of the patients with hystero graphically demonstrated involvement of the upper part of the cervix only, curettage was positive in 22 %. When the upper two thirds of the cervix was involved, curettage was positive in 43 % and when the total cervix was involved 6 out of 8 were positive.

Thus, the more the tumour engaged the cervix roentgenologically, the more often cervical curettage was positive.

The extended microscopic examination of the cervical curettings was more often positive when hystero graphy also suggested cervical involvement (Table 20).

It seems probable that hystero graphy gives a detailed and rather accurate information on the tumour extent in the uterine body and cervix. It thus supports NORMAN's (1950) assertion that 'hystero graphy is better able to reveal endocervical extension of the growth than instrumental exploration'. It cannot however yield information on infiltration in the myometrium.

Flow of contrast medium into tubes and vascular backflow

Flow of contrast medium into the tubes and vascular backflow may be related to extrauterine dissemination of the tumour. The passage of contrast out into the tubes or vessels was considered as likely if it occurred at the first or second hystero graphy. In most cases it occurred at the first examination before the beginning of treatment. Contrast medium passed into the tubes in 55 cases and into the vessels in 23 at the second examination. Contrast medium flowed out into the tubes in 434 (73 %) patients (Table 21). Vascular backflow was observed in 173 (29 %) patients.

563 cases were studied for any correlation between the tubar or vascular flow of contrast medium and the histologic tumour grade (Table 22). The contrast medium did not so often flow into the tubes in poorly differentiated tumours (grade 3 + 4, $p < 0.01$). The frequency of vascular backflow did not significantly differ in patients with tumours of poor or high differentiation.

Table 22

Frequency of contrast medium in tubes and vascular system in patients with adenocarcinoma of varying degree of differentiation

Extrauterine flow	Histologic grade			
	1	2	3	4
None	52 (18 %)	36 (19 %)	15	9
			24 (31 %)	
Into tubes irrespective of vascular backflow	223 (76 %)	143 (75 %)	32	9
			41 (53 %)	
Vascular backflow irrespective of flow into tubes	82 (28 %)	55 (29 %)	23	3
			26 (34 %)	
Total	294	192	57	20

According to KELLER (1948) escape of contrast medium via the tubes into the abdominal cavity is rare, usually because the tubes are obstructed in patients with carcinoma of the uterine body. DAVIDS (1953) also claimed that contrast flow into the tubes is very rare. He used, however, very small amounts of contrast medium to avoid extra-uterine flow. TARLOWSKA et coll. (1970) reported tubar flow in 28 % despite extreme care to avoid it. NORMAN (1950) reported passage of contrast medium through the tubes in 46 %.

In the present investigation contrast medium was seen in the tubes in 73 %. The absence of tubal contrast flow in cases with poorly differentiated tumours may be because they tend to infiltrate underlying tissues with a consequently greater chance of tubal occlusion (CORSCADEN & TOVELL 1954, LINDGREN 1957, GUSBERG et coll. 1960, BOUTSELIS et coll. 1963, CLIMIE & RACHMANINOFF 1965, AUSTIN & MACMAHON 1969, CHEON 1969, NG & REAGAN 1970, VONGTAMA et coll. 1970). Since all the patients in the present investigation received pre-operative radiation therapy the degree of myometrial infiltration was not examined.

Vascular backflow was reported by DAVIDS (1953) to occur in 2 % in a 'mixed material' (patients seen for sterility and uterine bleeding). OBOLENSKY & ZÜRCHER (1964) observed this phenomenon in 40 % compared with a frequency of only 2 % in patients without any tumours. ZSOLNAI & NYRÖ (1968) reported 7.4 % reflux among patients with tumours.

TARLOWSKA et coll. (1970) reported vascular backflow in 14 %. In 22 % out of 58 patients it was combined with a tumour type named by these authors as

'adenocarcinoid', considered as more malignant and with a very vulnerable vascular stroma, while in 13 % out of 255 patients it was combined with other tumour types. In the present investigation no significant correlation was found between the frequency of backflow and the histologic grading of the tumours.

Complications

Infection

General

Infectious complications were divided into two main groups according to severity. When multiple infections occurred in cases treated more than once the most severe reaction always was recorded. Antibiotics were not given prophylactically.

Definitions

Minor complications

A. Body temperature of at least 38°C for less than 3 days following hystero-graphy or intracavitary radiation therapy. Such a complication inconvenienced the patient but little, and did not affect the routine treatment or prolong the patient's stay in hospital.

B. Body temperature of at least 38°C for 3 days or more. This meant prolonged hospitalisation but did not affect the course of treatment.

Major complications

A. Infectious complications requiring removal of the radium capsules. When a patient got chills or body temperature above 38.5°C or increasing tenderness in the lower abdomen, treatment was interrupted. The symptoms soon disappeared and treatment was resumed.

B. Salpingitis. This complication occurred either immediately after hystero-graphy or insertion of the capsules or within the first 2 months of the end of treatment.

Patients examined with fractional curettage and hystero-graphy

Infectious complications were distributed among all the patients who had undergone hystero-graphy including those with technically unsuccessful examination or in cases with no signs of a tumour.

The records of 594 of the 606 patients in the series were available, but in 12 (2 %) the data were insufficient and these cases were excluded. In the records

Table 23*Infectious complications among 594 patients examined with hystero-graphy*

	No. of patients		Total	Per cent
	Reaction immediately after hystero-graphy	Reaction during treatment		
No complications			546	92
Mild complications				
A (temp. $\geq 38^{\circ}$ C for less than 3 days)	5	18	23	6
B (temp. $\geq 38^{\circ}$ C for 3 days or more)	4	6	10	
Severe complications				
A (capsules removed)		3	3	<1
B (salpingitis)	2	10	12	2
Total	11	37	594	101

of 92 % of the patients no infectious complications were noted, in 6 % only mild complications (Table 23) and in 3 % major complications.

Of the 23 patients whose minor reactions did not prolong hospitalisation, 1 got chills immediately after the roentgen examination, and 4 a slight temperature rise in the morning after the hystero-graphy.

In 4 out of 10 patients with a minor reaction and subsequent extended hospitalisation the symptoms and signs appeared immediately after the roentgen examination. Of these 2 got chills immediately after hystero-graphy and 2 mild fever the morning after. In 1 of these patients the hystero-graphy was performed one month after the end of radiation therapy to assess the progress of healing.

In 3 patients the capsules had to be removed because of severe complications. None of them had been examined with hystero-graphy before the actual radium treatment. Of 12 patients with salpingitis, the complication occurred immediately after the second hystero-graphic examination in 1 patient, who had to be operated upon in the acute stage. In 1 patient salpingitis was diagnosed 2 months after hystero-graphy performed to assess the rate of healing after the end of treatment. In 6 patients salpingitis appeared immediately after treatment. Two of these patients were operated upon in the acute inflammatory stage.

On return of the patients for the second course of radium treatment, 3 were found to have clinical signs of salpingitis. Two of them were operated upon. In 1 patient salpingitis was diagnosed at follow-up 2 months after the end of irradiation.

Table 24
Infectious complications among 154 patients not examined with hystero-graphy

	No. of patients	Per cent
No complications	139	90
Mild complications		
A (temp. $\geq 38^{\circ}$ C for less than 3 days)	4	4
B (temp. $\geq 38^{\circ}$ C for 3 days or more)	2	
Severe complications		
A (capsules removed)	6	4
B (salpingitis)	3	2
Total	154	100

Patients examined with curettage only

Of 158 patients who had been examined with curettage only, data about infectious complications were available in 154.

Ninety % had no infectious complications, 4 had mild complications with a rise in body temperature to at least 38° C for less than 3 days. In 2 other cases a rise in body temperature prolonged hospitalisation.

Nine (6 %) of the patients had major complications (Table 24) with subsequent premature removal of the capsules in 6 of them. In 3 patients salpingitis occurred immediately after treatment. One of these patients had to be operated upon in the acute stage.

Discussion

The frequency of infectious complications following hystero-graphy ranges from 0.25 to 3 % (KJELLBERG 1942, 1.2 %, NIELSEN 1946, 0.25 %, RYDÉN & WESTGREN 1954, 1 to 3 %, JOHNSSON 1956, 0.3 to 0.6 %). Curettage is often performed soon after the roentgen examination, and consequently it is difficult to analyse to what extent the roentgen examination per se induced salpingitis.

Reports on infectious complications after hystero-graphy of patients with carcinoma of the uterine body are scanty. NORMAN (1950) reported fever after 4 of 411 hystero-graphies and DAVIDS (1953) found few complications in a mixed series of 3 000 cases, including carcinoma of the uterine body. According to GRAZIANI & CATURANI (1961), hystero-graphy rarely causes complications.

YURUKOV (1964) reported no 'major complications' after hystero-graphy of 100 women with carcinoma of the uterine body.

Only a few publications are available on the frequency of infectious complications following insertion of capsules in the uterine cavity.

KOTTMEIER (1954) reported pelvic peritonitis in 1.2 % in a series of 1 032 cases and an equal frequency of sepsis and fever of more than 3 days in 2.6 %.

DÍAZ LLORENTE (1963) found a slight rise in body temperature in 14 of 118 patients following the local use of antibiotics in the vagina. Of 150 cases where antibiotics were not used, fever occurred in 31. In 20 of these cases it was necessary to interrupt radiation therapy.

KARLSTEDT (1968) found a rise in body temperature to more than 38° C for at least 2 days after intracavitary irradiation in 36 of 2 400 treatments and pyometra in 52.

The frequency of complications that occurred in this material is close to the figures given by KOTTMEIER. Of the 33 patients in the hystero-graphic series who developed minor complications, 9 appeared immediately after hystero-graphy. In 2 of the 12 patients who developed salpingitis the complication appeared immediately after hystero-graphy. No increase occurred in the frequency of infectious complications in those cases where hystero-graphy had been performed the day before intrauterine insertion of the capsules.

Though the two series were not comparable in respect of age-distribution, parity or number of operated patients, it appears that hystero-graphy means only an insignificant risk of producing infectious complications.

Spread of tumour

General

To assess the risk of tumour spread, all patients with recurrences or metastases were examined. Some of the patients had multifocal recurrences or metastases or both. Not all of the various sites were involved simultaneously. Of interest are adnexal metastases (ovaries and tubes) as well as remote metastases (lungs, liver, skeleton and peripheral lymph nodes).

The frequency of remote metastases was calculated on the basis of the entire material and that of adnexal metastases on unoperated cases. In addition, tumour growth in the adnexa were registered in the patients routinely operated upon. The lesions were diagnosed at physical and roentgenographic examinations, sometimes extended to include needle aspiration, biopsies and curettage. The number of patients who died from the tumours during the observation period was also noted (observation period 5—14 years).

Table 25

Recurrences and metastases after end of treatment of 606 patients examined hystero graphically

Vagina		Cervix uteri	Corpus uteri	Adnexa	Pelvic walls	Distant organs	No. of patients
lower half	upper half						
						+	37
					+	+	3
				+		+	2
			+			+	2
+	+					+	2
						+	1
					+		15
	+			+	+		1
					+		2
+			+		+		1
				+			14
			+	+			2
	+			+			1
			+				45
	+		+				3
+			+				1
		+					1
	+	+					2
+		+					2
+	+	+					2
	+						4
+	+						2
+							3
Total							148

Recurrences, metastases and deaths from carcinoma

Patients examined with curettage and hystero graphy. The number of recurrences and that of metastases were calculated on the basis of all patients examined with hystero graphy even when the examination had been technically unsuccessful, did not have any tumour, or when the films could not be retrieved. Of the 606 patients, 148 (24 %) got a recurrence or metastases. The sites of the recurrences and metastases are given in Table 25.

Table 26

Recurrences and metastases after end of treatment of 158 patients not examined with hystero-graphy

Vagina		Cervix uteri	Corpus uteri	Adnexa	Pelvic walls	Distant organs	No. of patients
lower half	upper half						
						+	12
				+		+	1
			+	+		+	1
			+			+	2
	+					+	2
					+		5
				+			2
			+	+			2
			+				16
	+						3
+							2
Total							48

Remote metastases only, were noted in 37 (6 %) of the patients. This type of spread, also in combination with recurrences or other metastases, was noted in 47 (8 %) of the patients.

In 34 of these patients the remote metastases were situated in the lungs or pleurae. Three also had metastases in the supraclavicular fossa, 3 in the skeleton, 1 in the inguinal region and 1 in the cerebrum. Five patients had metastases demonstrable only in the skeleton; 3 only in the supraclavicular fossa, 1 in the supraclavicular fossa and the inguinal reg.; and 3 only in the liver. One patient had metastases of unspecified site.

Adnexal metastases alone occurred in 14 of 279 (5 %) patients. Routine operation revealed involvement of the adnexa in 20 (6 %) of further 327 patients. Adnexal metastases were thus totally seen in 34 (6 %) of 606 patients. Together with other sites of metastases or recurrences the figure was 40 (7 %) of 606 patients. During the observation period 118 (19 %) of the patients died of their disease.

Patients examined with curettage only. Of the 158 patients, 48 (30 %) had a recurrence and/or metastases (Table 26). Twelve (8 %) of the patients had only remote metastases. Combined with recurrences or other metastases the number of cases arose to 18 (11 %). Metastases confined to the adnexa, were

Table 27

Frequency of flow of contrast medium into tubes or vascular backflow among patients with and without recurrences or metastases

Extrauterine flow	No. of patients without recurrences or metastases	Per cent	No. of patients with recurrences or metastases	Per cent
Into tubes only	255	57	56	39
Vascular backflow only	36	8	14	10
Into tubes + vascular backflow	93	21	30	21
None	66	15	42	30
Total	450	100	142	100
Into tubes irrespective of vascular backflow	348	77	86	61
Vascular backflow irrespective of flow into tubes	129	29	44	31

found in 2 of 92 cases and revealed in further 6 of 65 cases at routine operation. Thus 8 (5 %) of 158 patients had metastases only in the adnexa. In combination with other metastases or recurrences adnexal metastases were found in 12 (8 %) of 158 cases. During the observation period 44 (28 %) of the patients died of their disease.

Recurrences and metastases versus the finding of contrast medium in the tubes and vascular backflow

The frequency of contrast in the tubes or in the vessels in 592 patients of which 142 patients had recurrences and metastases is given in Table 27.

Contrast medium thus was seen in the tubes less often ($p < 0.01$) in patients with recurrences and metastases. The frequency of vascular backflow was the same among patients with recurrences and metastases as among them without.

Contrast medium into the tubes was seen less often in cases with remote metastases ($p < 0.01$), but the frequency was the same in patients with adnexal metastases. The frequency of vascular backflow was the same in patients with remote and adnexal metastases as among those who were free of symptoms.

Frequency of recurrences and metastases in relation to number of hystero-graphic examinations

Of the 606 women examined hystero-graphically, 156 were examined once and 450 more than once. Hystero-graphy was made only once in patients who had

been operated upon after the first intracavitary treatment. In the cases with only small or no lesions demonstrable at the first hystero-graphic examination, this was, as a rule, not repeated. In addition, technical mishaps sometimes precluded a second hystero-graphy.

41 (26 %) of the cases with recurrences and metastases had been examined only once and 107 (24 %) examined twice or more. Thus, no difference was found between these 2 groups.

Of the women who had been hystero-graphically examined once, 6 (4 %) had only remote metastases and 8 (5 %) had also other metastases or recurrences. The corresponding figures for patients examined more than once were 31 (7 %) and 39 (9 %).

The number of patients with adnexal metastases only (including also adnexal metastases found at routine operations) and the number of cases with adnexal and other metastases or recurrences among those examined only once were 8 (5 %) and 8 (5 %), respectively. The corresponding figures for patients examined twice or more were 26 (6 %) and 32 (7 %).

The investigation thus revealed an increased frequency of remote metastases and adnexal metastases in patients examined hystero-graphically twice or more. The difference was, however, not significant.

Discussion

Carcinoma of the uterine body grows relatively slowly and is susceptible to different forms of treatment.

The tumour has a tendency to metastasise to the adnexa and to set up remote metastases. The frequency of remote metastases given by various authors varies considerably (20 % by FINN 1950, 11 % by TARLOWSKA 1964). BUNKER (1959), JAVERT & HOFAMMANN (1952) found pulmonary metastases in 14 % and 9 %, respectively. This variation is due partly to differences in the series, in the examination method used, and in the length of the observation period.

For the same reasons also the frequency of adnexal metastases varies widely from series to series. (JAVERT & HOFAMMANN 17 %, RUNGE & ZEITZ 1956 13 %, NOGALES et coll. 1964 in 23 %).

As previously mentioned, some examiners are reluctant to perform hystero-graphy as they fear that the examination might cause spread of the tumour (CROSSEN 1937, TASCH 1941, MACKENZIE 1953, STUDDIFORD 1953).

The greatest risk is believed to be tumour dissemination via the tubes. LYNCH & DOCKERTY (1945) analysed this problem histologically in surgical specimens and concluded the tumour rarely spreads via the tubes. Among 21 patients operated upon because of carcinoma of the uterine body DAHLE (1956) found

malignant cells in the tubes in 11 cases. In 6 of these patients he also found malignant cells in the irrigation fluid of the fossa of Douglas. He pointed out, however, that he did not know whether these cells were viable or not. HÖEG (1956) revealed malignant cells in the washings of the fossa of Douglas in 6 out of 20 cases of carcinoma of the uterine body. Saline irrigation of the tubes was performed in 25 cases. In 15 of these she found malignant cells. Such cells were seen in both tubes in 8 of these cases.

MARCUS (1962) reported 15 patients operated upon because of carcinoma of the uterine body. He found malignant cells in the peritoneal irrigation fluid in 3, possible malignant cells in 10 and no malignant cells in 2. He also pointed out that 'even if one accepts the contingency of tubal transmission of malignant cells the potential for or actual implantation of such cells remains unproved'.

ALENIKOVA (1967) found malignant cells in the peritoneal irrigation fluid from 3 patients, in fluid from the left tube in 3 patients and from both tubes and peritoneal irrigation fluid in 1 patient in a series of 36 patients. CREASMAN & RUTLEDGE (1971) reported a higher frequency of atypical cells in peritoneal washings from patients with more advanced tumours. In cases where no tumour was found or the tumour was confined to the endometrium abnormal cells were found in 2 out of 68 and in 2 out of 58 respectively. When the myometrium was involved or when the tumour had spread beyond the uterus, the corresponding figures were 3 out of 27 and 12 out of 30, respectively. The number of patients living and well after 4 years was lower when the cytologic findings were abnormal.

Also the risk of spread via the vascular system has been stressed. ROBERTS et coll. (1960) reported malignant cells in the circulating blood during curettage in 4 out of 5 patients with malignant tumour of the endometrium.

SOOST (1961) demonstrated malignant cells in the circulating blood in 7 out of 29 patients with carcinoma of the uterine body. In his opinion only a very slight increase of spill of malignant cells occurred in association with surgical intervention (curettage, intracavitary radiation therapy and laparotomy). He, too, stressed the difficulty to recognise malignant cells in circulating blood and that it is not yet known whether the demonstrable tumour cells are capable of setting up metastases.

COLE (1962), however, reported a 5-year survival of 8 % in an operated series with circulating malignant cells at the time of the operation and a 5 year survival rate of 32 % for those patients in whom no such cells had been demonstrated at the time of operation.

Out of 4 cases of carcinoma of the uterine body WIMHÖFER et coll. (1963) reported malignant cells in the blood before operation in one and during operation in 3.

Thus, tumour cells may be disseminated via the tubes and via the vessels. At hystero-graphy contrast medium entered these structures in some of the cases and may have enabled such dissemination. If contrast medium is demonstrated in the hystero-gram it must be present in a relatively high concentration. It may therefore be assumed that small amounts of contrast medium escaped into the tubes and vessels also in women without roentgenologically demonstrable findings.

Moreover, contrast medium is rapidly absorbed, and the hystero-grams depict only the situation of a few moments. This limits the value of correlating metastases to the flow of medium out into the tubes and gives but little information about the possible risk of dissemination of tumour cells by hystero-graphy. Certainly single cases have been published where operation some time after hystero-graphy revealed metastases in the ovaries and fossa of Douglas. Such single observations can, however, not be accepted as evidence that roentgen examination caused the spread (KOTTMEIER 1959).

In the present investigation recurrences and metastases were recorded almost as often (24 %) in patients who were examined hystero-graphically as among those who were not (30 %). Fewer patients died from the tumour in the group examined with hystero-graphy (19 %) than in the remainder (28 %). This difference can probably be explained by the fact that the latter group contained a larger percentage of elderly patients and patients in a poor general condition.

TARLOWSKA et coll. (1970) reported distant metastases in 6.7 % of 313 patients who had been examined with hystero-graphy, compared with 10.9 % of 386 patients who had not. The figures agree well with them in the present investigation, viz. 8 % of 606 and 11 % of 158.

In the two series the groups examined and not examined hystero-graphically are not comparable. In TARLOWSKA's material the two groups differed in respect of the methods of treatment used and in the time interval between the two groups (1947—1952 for the group not examined and 1952—1962 for the group examined hystero-graphically). The differences in this respect between the two groups in the present material have been described on page 27.

TARLOWSKA et coll. reported remote metastases in 5.2 % of 210 patients where no contrast passed into the tubes or the vessels and in 5.2 % of 58 where contrast entered only the tubes, but in 15.6 % of 45 patients with demonstrable contrast medium in the vessels. Of these 45 patients, 64 % were judged as not being cured from their disease, while the corresponding figure for 58 patients with contrast medium only in the tubes was 36 %, and for 210 patients without contrast medium in the tubes or vessels 39 %. In the present material 12 % of 108 patients without contrast flow in the tubes or vessels had remote metastases, 6 % of 434 with contrast medium in the tubes and 9 % of 173 with contrast medium in the vessels. The frequency of death from the disease in this material

was 31 %, 16 % and 19 %, respectively.

The explanation why recurrences and metastases were less common in cases where contrast medium had been demonstrated in the tubes is that the tumour had involved a relatively small area of the endometrium, while in those where no contrast medium was found in the tubes, the tumour had affected large parts of the endometrium and probably occluded the internal orifices of the tubes.

In the present investigation no special measures were undertaken to prevent the passage of contrast medium into the tubes or vessels at hystero-graphy. This is apparent from the frequency with which such passage occurred in the tubes (73 %) and in the vessels (29 %) compared with 28 % and 14 % in TARLOWSKA's material. Differences in the examination technique can probably explain the difference in the frequency of remote metastases in relation to the passage of contrast medium into the tubes in the two materials.

In the present material the frequency of remote metastases was not higher among the cases in which medium had passed into the vessels. This may also be explained by the roentgen technique. If contrast medium passed into the vessels despite special care (TARLOWSKA) it is probable that the tumour and its vascular bed are vulnerable and that even small trauma may be sufficient to facilitate vascular spread. As pointed out by TARLOWSKA the occurrence of contrast medium in the vessels is probably not the cause of an increased frequency of metastases but a sign of biologically active tumours with a strong tendency to spread.

With the technique used at hystero-graphy in the present series such more active tumour types may have been masked by the higher frequency of contrast medium in the vessels owing to the less gentle technique used.

The frequency of metastases among patients examined only once with hystero-graphy did not differ significantly from that among patients examined more than once. Since the two groups are not comparable, it is not possible to make a definite statement if repeated hystero-graphy implies an increased risk of metastases or not.

Though the different groups are not strictly comparable, it seems reasonable that hystero-graphy carries only an insignificant risk of producing metastases.

Curettage may also imply a risk of spread of tumour via the tubes and via the vessels (SAMPSON 1934, MILLER 1959, HENRIKSEN 1960, WALL et coll. 1967, DIDDLE 1967) but it is not possible to assess curettage and tumour spread in the present material because all patients were scraped primarily.

Residual tumour and recurrences in the uterus

Extent of tumour hystero graphically

Residual tumours among 305 patients who had been treated with preoperative irradiation and surgery

The hospital records were incomplete and not useful in 6 cases. The frequency of residual tumour in the uterus tended to increase successively with the extent of cervical involvement (Table 28). The difference was, however, not significant ($p > 0.05$).

Also the frequency of residual tumour in the cervix tended to increase successively with the extent of cervical involvement, but the number of cases with residual tumour was too small to allow statistical analysis.

Recurrences in 267 patients who received radiation therapy only

Table 29 summarises the demonstrated recurrences. As judged clinically 64 of the cases were operable (page 20). The operative findings are given in Tables 30, 31 and 32. The frequency of recurrences seems to be independent of the extent of primary involvement of the corpus and cervix. When also the upper two thirds or more of the cervix are involved the frequency of recurrences was somewhat, but not significantly ($p > 0.05$) higher.

The frequency of cervical recurrences tended to increase successively with the extent of cervical involvement. The number of recurrences in cases with the tumour primarily confined to the corpus was, however, too small to allow statistical analysis. The difference in frequency of recurrences in cervix between patients with tumour primarily localised to the corpus and the upper third of the cervix and those involving the upper two thirds or more of the cervix was not significant ($p > 0.05$).

Residual tumour and recurrences in the uterus among 572 patients

The frequency of residual tumour/recurrences in the uterus was the same whether the growth was confined to the corpus or involved also the upper third of the cervix and somewhat, but not significantly, ($p > 0.05$) higher when the lesion involved the upper two thirds or more of the cervix (Table 33).

The frequency of residual tumour/recurrences in cervix tended to increase successively with the extent of cervical involvement. The number of residual tumour/recurrences in cervix when the tumour was primarily confined to the corpus still was too small to warrant statistical analysis. The difference in

Table 28*Residual uterine growth among 305 patients treated with preoperative irradiation and surgery*

Site of tumour	No. of patients	Residual growth in	
		Uterus	Cervix
	155	46 (30 %)	1 (< 1 %)
	109	39 (36 %)	4 (4 %)
	41	19 ($\approx$ 46 %)	5 ($\approx$ 12 %)

Table 29*Recurrences among 267 patients given radiation therapy only. The figures include clinical findings in patients given radiation therapy only, as well as histologic findings in such patients operated upon because of possible recurrences or metastases*

Site of tumour	No. of patients	Recurrences in	
		Uterus	Cervix
	133	23 (17 %)	2 (2 %)
	92	14 (15 %)	5 (5 %)
	42	9 ($\approx$ 21 %)	5 ($\approx$ 12 %)

frequency of residual tumour/recurrences in cervix in cases with involvement of the upper third of the cervix and with involvement of the upper two thirds or more of the cervix was significant ($p < 0.05$).

Table 30

Clinical and histologic findings at operations of possible recurrences or metastases in 31 patients with tumour hystero graphically confined to the uterine body

No carcinoma	Carcinoma of					No. of patients
	Endo- metrium	Myo- metrium	Adnexa	Peri- toneum	Cervix	
	+	+			+	1
				+		1
		+	+	+		1
	+	+		+		1
			+			3
	+	+				12
	+					1
+						11
Total						31

8 patients with assumed recurrence in the uterus preoperatively had histologic signs of carcinoma in the operative specimens.
2 patients with assumed ovarian metastases preoperatively had no histologic signs of carcinoma of the ovaries.
1 patient with assumed pelvic metastases preoperatively had no such growth at operation.

Table 31

Clinical and histologic findings at operations of possible recurrences or metastases in 22 patients with uterine tumour hystero graphically involving also the upper third of cervix

No carcinoma	Carcinoma of					No. of patients
	Endo- metrium	Myo- metrium	Adnexa	Peri- toneum	Cervix	
	+	+	+		+	2
	+	+			+	2
			+	+		1
		+	+	+		1
			+			1
	+	+	+			1
	+		+			1
	+	+				6
	+					2
+						5
Total						22

Table 32

Clinical and histologic findings at operations of possible recurrences or metastases in 11 patients with uterine tumour involving also the lower two thirds or more of the cervix hystero graphically

No carcinoma	Carcinoma of					No. of patients
	Endo-metrium	Myo-metrium	Adnexa	Peri-toneum	Cervix	
	+	+	+		+	1
	+	+			+	2
				+		1
	+	+				4
+						3
Total						11

2 patients with tumour growth in the cervix histologically had no signs of such tumour preoperatively.

2 patients with assumed recurrence in the uterus preoperatively had no histologic signs of carcinoma in the operative specimens.

1 patient with assumed ovarian metastases preoperatively had no histologic signs of carcinoma of the ovaries.

Extent of tumour as judged by curettage

Residual tumour among 305 patients who had been treated with preoperative irradiation and surgery

The hospital records were incomplete and could not be used in 6 cases. The frequency of residual tumour in the uterus was higher in stage II than in stage I (Table 34). The difference was significant ($p < 0.05$). The frequency of residual tumour in the cervix tended to be higher in stage II than in stage I. The number of cases with residual tumour in stage II was, however, too small to allow statistical analysis.

Table 31 (cont.)

4 patients with tumour growth in the cervix histologically had no signs of such tumour preoperatively.

3 patients with assumed recurrence in the uterus preoperatively had no histologic signs of tumour in the operative specimens.

2 patients with assumed ovarian metastases preoperatively had no histologic signs of carcinoma of the ovaries.

2 patients with assumed ovarian metastases preoperatively had also carcinoma of the uterus.

Table 33*Residual uterine growth and recurrences among 572 patients*

Site of tumour	No. of patients	Residual growth and recurrences in	
		Uterus	Cervix
	288	69 (24 %)	3 (1 %)
	201	53 (26 %)	9 (4 %)
	83	28 (34 %)	10 (12 %)

Table 34*Residual uterine growth among 305 patients treated with preoperative irradiation and surgery*

Site of tumour	No. of patients	Residual growth in	
		Uterus	Cervix
Stage I			
	261	82 (31 %)	6 (2 %)
Stage II			
	44	22 ($\approx$ 50 %)	4 ($\approx$ 9 %)

Recurrences in 267 patients who received radiation therapy only

Table 35 summarises the demonstrated recurrences. Sixty-four of these were regarded as operable (page 20). The operative findings in these cases are given in Tables 36 and 37. The frequency of recurrences in the uterus was independent of the extent of tumour in corpus and cervix.

The frequency of recurrences in the cervix tended to be higher in stage II than in stage I. The number of cases with recurrences in stage II was, however, too small to allow statistical analysis.

Table 35*Recurrences among 267 patients given radiation therapy only*

Site of tumour	No. of patients	Recurrences in	
		Uterus	Cervix
Stage I 	224	38 (17 %)	8 (4 %)
Stage II 	43	8 ($\approx$ 19 %)	4 ($\approx$ 9 %)

Table 36*Clinical and histologic findings at operations of possible recurrences or metastases in 54 patients in stage I*

No carcinoma	Carcinoma of					No. of patients
	Endo-metrium	Myo-metrium	Adnexa	Peri-toneum	Cervix	
	+	+	+		+	2
	+	+			+	4
				+		1
			+	+		1
		+	+	+		1
	+	+		+		1
			+			4
	+	+	+			1
	+	+				18
	+					3
+						18
Total						54

4 patients with tumour growth in the cervix histologically had no signs of such tumour preoperatively.

12 patients with assumed recurrence in the uterus preoperatively had no histologic signs of tumour in the operative specimens.

5 patients with assumed ovarian metastases preoperatively had no histologic signs of carcinoma of the ovaries.

1 patient with assumed pelvic metastases preoperatively had no such growth at operation.

1 patient with assumed ovarian metastases preoperatively had also carcinoma of the uterus.

Table 37

Clinical and histologic findings at operations of possible recurrences or metastases in 10 patients in stage II

No carcinoma	Carcinoma of					No. of patients
	Endo-metrium	Myo-metrium	Adnexa	Peri-toneum	Cervix	
	+	+	+		+	1
	+	+			+	1
				+		1
		+	+	+		1
	+		+			1
	+	+				4
+						1
Total						10

- 2 patients with tumour growth in the cervix histologically had no signs of such tumour preoperatively.
- 1 patient with assumed recurrence in the uterus preoperatively had no histologic signs of tumour in the operative specimens.
- 1 patient with assumed ovarian metastases preoperatively had also carcinoma of the uterus.

Residual tumour and recurrences in the uterus among 572 patients

The frequency of residual tumour/recurrences in the uterus was higher in stage II than in stage I (Table 38) but the difference was not significant ($p > 0.05$). Even the frequency of residual tumour/recurrences in the cervix was higher in stage II than in stage I and in this respect the difference was significant ($p < 0.01$).

Histologic grading

The frequency of residual carcinoma or recurrences in uterus is grouped according to degree of differentiation of the tumour in Table 39. The frequency of residual carcinoma after preoperative radiation therapy did not vary with the degree of tumour differentiation.

In the group of patients that primarily received only irradiation, recurrences in the uterus were more often of grade 1 than of lower differentiation. But the difference was not significant.

Table 38*Residual uterine growth and recurrences among 572 patients*

Site of tumour	No. of patients	Residual growth and recurrences in	
		Uterus	Cervix
Stage I			
	485	120 (25 %)	14 (3 %)
Stage II			
	87	30 (34 %)	8 (9 %)

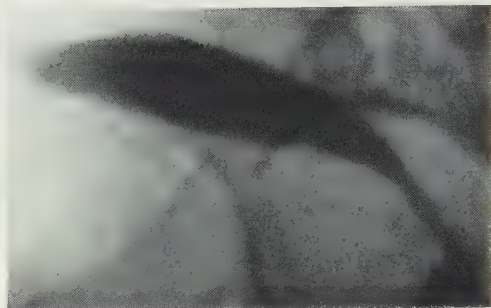
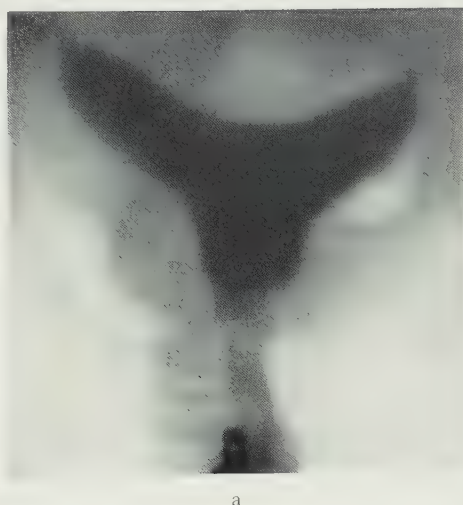
Table 39*Residual and recurrent carcinoma after radiation therapy*

	Histologic grading			
	1	2	3	4
Residual carcinoma after preoperative irradiation	55/131 (42 %)	39/97 40 (%)	15/31	18/37 3/6
Recurrence after irradiation	34/142 (24 %)	11/73 15 (%)	2/22	5/34 3/12

Discussion

Residual carcinoma in the uterus after intracavitary radiation therapy was found with varying frequency at hysterectomy (see page 7). An explanation may be the difficulty to get a well defined absorbed radiation dose in the uterus with the intracavitary technique.

The distribution of the dose around a tandem can be easily calculated and thereby also the dose absorbed by the uterus. The size and configuration of the uterus as well as the position of the applicator in the uterus must, however, be known (HELD 1934, NOLAN & ARNESON 1943). When a tandem is used the absorbed dose in the cervix is high while that in the uterine horn is much lower. FREED & PENDERGRASS (1954) gave the ratio max/min for tandem as 4.7 : 1 calculated 'about the external surface of a normalized uterus'.



b

Fig. 9. Uterine cavity with prominent horns. Hystero-gram 3 weeks after end of first course of intracavitary irradiation. Residual carcinoma in lower part of corpus and large parts of cervix. a) Frontal view. b) Lateral view.

To obtain a more even distribution of the absorbed dose a number of modifications of the tandem have been devised. 'Das Radiumbukett und den Triangel' by DIETEL (1933), 'Radiumring' by KAPLAN (1942), 'Trident' by CORSCADEN & TOVELL (1954), 'Flexible linear source' by STRICKLAND (1965), 'Y-applicator' by SCHMITZ & SCHMITZ (1935), 'Hysterostat' by FRIEDMAN (1940), 'Wire technique' by CROSSEN (1946). The ratio max/min by the three last mentioned groups varies between 4.3 : 1—3.1 : 1 according to FREED & PENDERGRASS.

By using multiple applicators it is possible to obtain a more even distribution of the absorbed dose. MARTIN (1940) used 'Hinged applicators', while HEYMAN et coll. (1941), HOWE & JENNINGS (1947), NOLAN & STEELE (1948) used the packing technique. FREED & PENDERGRASS gave the ratio max/min 1.4 : 1 with this (HEYMAN) technique calculated 'about the external surface of a normal-sized uterus'.

BECKER & SCHEER (1952) used ^{60}Co -sources enclosed in spheres or ovoids ('Cobalt pearls') 4—7 mm in diameter. The ratio max/min with this technique calculated in the way described above was given by BICKENBACH et coll. (1955) as 2.5 : 1.

The absorbed dose 'about the external surface of a normal-sized uterus' (about 1.5 cm from the nearest applicator — HEYMAN et coll. 1941, KJELLGREN & JONSSON 1965) thus varied with the position of the measuring point on the outer contour of the uterus (cervix-uterine horn-fundus).

Determinations have, as a rule, been made in uteri of varying size but of

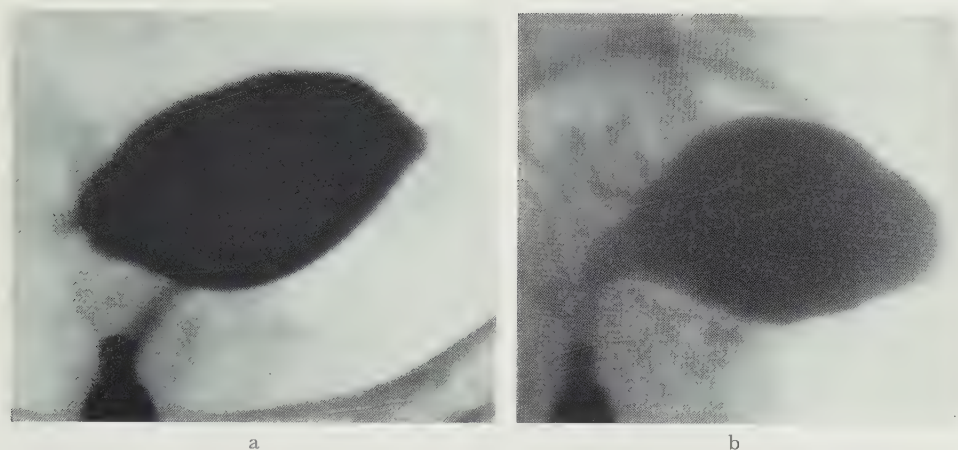


Fig. 10. Spherical uterine cavity. Hystero-gram 3 weeks after first course of intracavitary irradiation. No residual carcinoma. a) Frontal view. b) Lateral view.

'normal appearance' (HEYMAN et coll. 1941, TARLOWSKA & SIKOROWA 1962, KJELLGREN & JONSSON 1965) and the treatment time has been determined from the number of applicators in the uterus.

SAMPSON (1934) and later NOLAN & STEELE (1948) also analysed the distribution of the dose about uteri deformed by tumour or myoma and state that 'irregularities in the size and shape of the uterus exert a general deleterious effect upon the effectiveness of multiple-capsul implantations of radium for the treatment of endometrial carcinoma'.

KUHN (1965) and KELLER et coll. (1971) showed that the absorbed dose in the uterine musculature varies largely with the size and shape of the uterine cavity.

The hystero-graphic technique showed that the shape of the uterine cavity varies widely irrespective of the local spread of the tumour in the uterus (NORMAN 1951). The hystero-grams in Figs 8, 9, 10 and 14 give examples of different shapes of the uterine cavity.

The absorbed dose in some points on the surface of 2 uterine cavities, one triangular, the other cylindrical, was calculated. In both cases the same number of applicators (capsules) (12) of the same size (ϕ 8 mm $\times$ 20 mm) and activity (10 mCi) were used. Figs 11 and 12 show the two diagrammatic arrangements of the capsules used.

The results reveal that the maximum dose calculated at a distance of 1.5 cm from the nearest applicator surface was more than 30 % larger for the plane

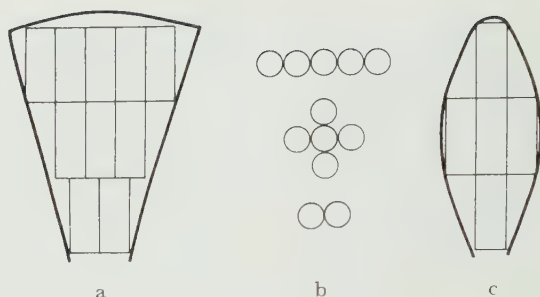


Fig. 11. Diagrammatic arrangement of capsules in a triangular uterine cavity. a) Frontal view. b) Distribution of capsules at three levels in a plane perpendicular to the frontal plane. c) Lateral view.

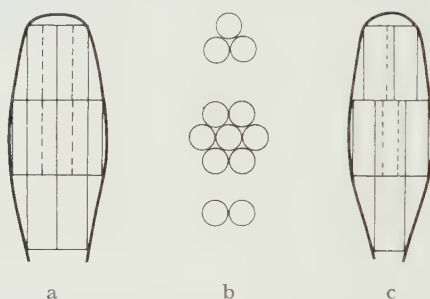


Fig. 12. Diagrammatic arrangement of capsules in a cylindrical uterine cavity. a) Frontal view. b) Disposition of capsules at three levels in a plane perpendicular to the frontal plane. c) Lateral view.

arrangement (Fig. 11). That these diagrams really reflect the disposition of the capsules in practice is exemplified in figures 13 and 15. The purpose of this calculation was only to demonstrate that it is not possible to calculate the absorbed dose in the uterus from the number of millicurie- or milligram hours with satisfactory accuracy, even if the number of capsules is known.

Calculation of the absorbed dose in the uterus in treatment with intracavitary radium using multiple applicators is thus uncertain.

Another factor which makes it difficult to evaluate the preoperative treatment is that the tumour extent is largely unknown (NOLAN & STEELE 1948, FREED & PENDERGRASS 1954). In about 10 % no tumour is left in the uterus after primary diagnostic curettage (page 33).

It is at present not possible to determine preoperatively the extent of myometric infiltration. This varies in primarily operated material. (LIU & MEIGS 1955 (47 %), LEFÈVRE 1956 (82 %), DAVIS 1964 (56.5 %), PRETTENHOFER

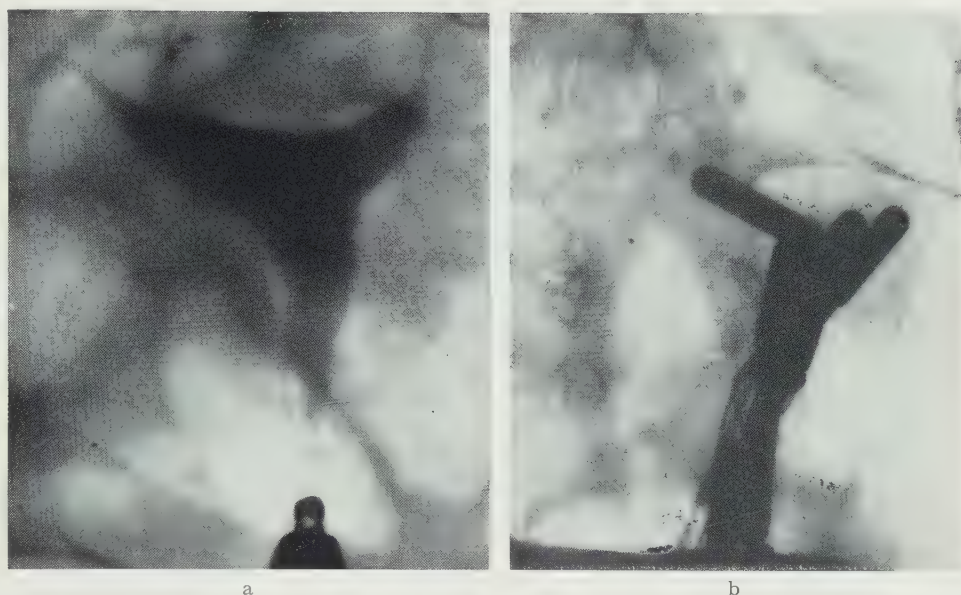


Fig. 13. Hystero-gram of a triangular uterine cavity. a) Frontal view. b) Owing to the smallness of the cavity eight small capsules ($\varnothing$ 4 mm $\times$ 20 mm) were used and placed in a plane arrangement.

1966 (88 %), HULBERT 1969 (61 %), LEWIS et coll. 1970 (84 %), SALL et coll. 1970 (51 %). Such variation should also be found in patients given pre-operative irradiation.

Another factor making it difficult to evaluate the effect of preoperative irradiation is the difficulty to decide microscopically whether the tumour cells exposed to ionising radiation are viable or not (STRICKLAND 1965) i.e. whether according to SUIT & GALLAGER (1964) these cells can 'proliferate and produce a recurrence of tumour'. These authors irradiated C_3H mice with spontaneous mammary carcinoma under condition of local tissue anoxia to varying dose levels.

The irradiated tumour was removed after 19—44 days. In all of these cases morphologically intact tumour cells were found. On isotransplantation, however, tumour growth was found in 10/12 that had received 4 000 rad and in 2 of 7 that had received 5 760 rad and in none of 18 that had received 7 600 rad and the authors concluded that for this 'animal tumour system the persistence of histologically intact cells in irradiated tissue does not indicate the probability of regrowth tumour'. This may also be true for other tumour systems.

The significance of the time of operation after irradiation for residual carcinoma has been discussed by HUNT (1956), who reported that resolution of



Fig. 14. Hystero-gram of a cylindrical uterine cavity. a) Frontal view. b) Lateral view.

carcinoma following radiation therapy requires six to twelve weeks, and that the earlier hysterectomy and microscopic examination are performed the higher will be the frequency of residual carcinoma. MARCIAL et coll. (1969) reported that after 6—8 weeks most of the expected tumour disappearance would have occurred.

In the present material 101 patients were operated upon within less than 1 month after the end of intracavitary treatment. Of these 56 (55 %) were found to have residual carcinoma in the uterus. Most of these patients, however, had received only one intracavitary treatment and thus the absorbed dose was smaller than in the rest of the material.

Among 204 patients operated upon within 1—12 months after treatment and given 2 intracavitary treatments or more residual malignant growth was found in the uterus in 49 (24 %). Among 267 patients given radiation therapy primarily recurrences in the uterus were noted in 46 (17 %) within an observation period of 5—14 years. Treatment was almost exactly the same as in the 1—12 months group.

The difference between the two groups may be ascribed partly to the fact that 15 (6 %) of the patients in the latter group had died from their disease without any registration of eventual recurrence.

The operated material and the material irradiated primarily were not randomised and primary differences might have been also in the spread of the tumour in the myometrium.

Reports on residual uterine carcinoma in various stages after preoperative

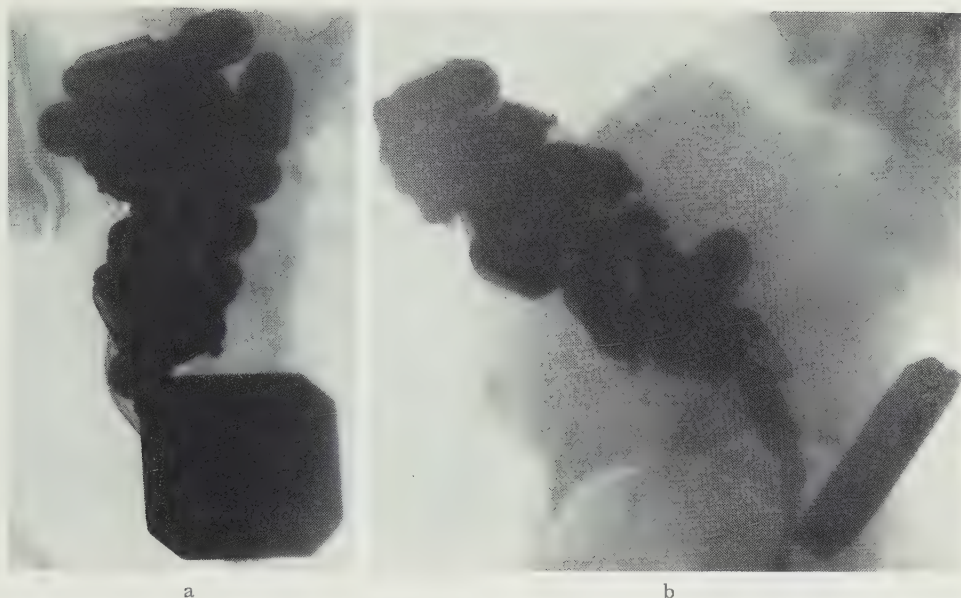


Fig. 15. Same case as in Fig. 14. a) Frontal view. b) Lateral view. Owing to the large uterine cavity twentyfour capsules enlarged by addition of jackets were used ($\varnothing$ 11 mm $\times$ 20 mm). Flat applicator in vagina.

irradiation are scanty. GEISLER & GIBBS (1968) reported 45 % of 94 patients with stage I. Four patients in stage II had all residual carcinoma in the uterus. Preoperative treatment was given by intracavitary radiation therapy alone or combined with external radiation.

MARCIAL et coll. (1969) reported residual cancer in the uterus in 19 of 39 patients in stage I and in 4 of 11 patients in stage II. The preoperative treatment was given as packing in some cases and occasionally of a tandem. In addition external treatment was given — calculated pelvic dose 4 000—5 000 R/45 days. The operations were performed 4 weeks or more after the end of radiation therapy.

DELCLOS et coll. (1969) reported residual carcinoma in the uterus in 30 % of 233 patients in stage I and in 40 % of 82 patients in stage II. They used the packing technique for stage I, and the packing technique or a tandem for stage II. Operation was performed 1—8 weeks after the end of radiation therapy.

KJELLGREN & MAGNUSSON (1970) using the packing technique reported 9 % residual carcinoma among 99 patients in stage I, of 31 patients in stage II 6 were found to have residual carcinoma 6—12 weeks after treatment.

In the present material residual carcinoma was found in 31 % of 261 patients in stage I and in about 50 % of 44 patients in stage II.



Fig. 16. Small tumour confined to the junction between body and cervix.

Though the materials are small, the tendency of residual carcinoma tended to be somewhat higher in stage II. This lends support to the opinion that in patients in stage II infiltration of the myometrium is more marked than in stage I (SCHWARTZ & BRUNSCHWIG 1957) (66 % and 22 %, respectively). Tumours in stage II may thus be more advanced not only because the tumour has been demonstrated in the cervix, but above all by the fact that it infiltrates the underlying tissue (PREM 1958).

This view is supported by observations by HEYMAN (1941) in a series of 'cancer corporis et colli uteri' (tumour of the body and cervix with or without spread beyond the uterus). According to him 44 % of 91 patients 'must be considered as advanced and inoperable on account of the spread of the growth beyond the uterus'. The corresponding figure for carcinoma of the uterine body was 17.4 % of 780 patients. His opinion was shared by KOTTMEIER (1954), ARNESON (1964) and LINDGREN (1957).

The reason why patients which have been classified as stage II, i.e. with tumour growth also in the cervix showed more marked myometrial infiltration, depends probably on the difficulty in estimating the condition of the cervix from curettings. Those patients in whom the underlying tissue is supposed to be infiltrated (the curette tears off large tissue fragments) and those where the tumour had also involved the lower part of the cervix will be over-represented in stage II. Superficial (endocervical) tumours, especially those in the upper part of the cervix, are liable to be missed by the curette, especially when the curettage is not primarily planned as fractional. HEYMAN (1949) shared this opinion.

Hystero-graphic evaluation of the local spread of the tumour supports this. A tumour involving the upper part of the cervix need not be so very extensive as in Fig. 3, for example, but may be relatively small and confined to the junction between the body and the cervix (Fig. 16).

Residual tumour was found in the uterus in 30 % of those women in whom hystero-graphy had shown involvement of the uterus alone; in 36 % of those in whom it had revealed involvement also of the upper third of the cervix and in 46 % of those in whom the cervical involvement extended also to the upper two thirds or more. The differences in frequency were not significant. The wide superficial spread (Fig. 5), however, suggests that it has also infiltrated the underlying tissue, even though the tumour may primarily have appeared multi-focal.

The results presented here thus suggest that in patients where curettage showed cervical growth (stage II) the tumours were more advanced (infiltrated underlying tissue) than when the malignant growth was confined to the corpus (stage I). This probably also applies to cases where malignant growth was hystero-graphically demonstrated in the upper two thirds or more of the cervix.

Cases primarily irradiated only presented no difference between stages I and II regarding the frequency of recurrences in the uterus, viz. 17 % of 224 and 19 % of 43 patients respectively. Neither was any difference in frequency of recurrences found between tumours involving the uterus only and those involving also the cervix as judged from the hystero-graphy.

These figures are close to those reported by KOTTMEIER (1954); 15 % recurrences in the uterus of 990 cases of carcinoma of the uterine body and in 12 % of 204 cases of 'cancer corporis et endocervicis uteri'. The frequencies were calculated on the basis of histologically verified findings at operation because of possible recurrence. The frequency of recurrences in cases of carcinoma corporis et endocervicis uteri was somewhat lower, probably because this classification includes also patients with growth beyond the uterus, i.e. technically inoperable cases. KARLSTEDT (1968) reclassified the material at the Radiumhemmet (KOTTMEIER 1954) with the use of criteria in 'Annual report 1964'. The frequencies of recurrences in the uterus were then 11 % for carcinoma of the uterine corpus stage I and 13 % for stage II calculated in the same way as that given above.

The frequency of residual carcinoma and recurrences in the cervix was higher for stage II than for stage I (9 % and 3 %, respectively).

Also when the extent of the tumour was judged hystero-graphically, the frequency of residual carcinoma and recurrence in the cervix was found to be higher when the primary tumour involved also the cervix (4—12 % and 1 %, respectively).

The method of irradiation used was thus followed by an equally high frequency of recurrences in uterus whether the primary tumour had involved the cervix or not. On the other hand, the frequency of residual tumour in the cervix increased in those cases where the primary tumour had involved the cervix.

This tendency was striking in those cases operated upon because of possible recurrence or metastases (Tables 30, 31, 32, 36, 37) especially when the local spread of the primary tumour had been judged hysterographically.

The results suggest that when planning radiation therapy of inoperable cases consideration should be given to the local spread of the primary tumour in the corpus-cervix. Especially hysterographic examination of tumour spread in the corpus and cervix is useful in planning of the therapy in the individual cases.

The cause of the difference between residual carcinoma and recurrences has been discussed previously. The results of the microscopic re-examination showed the same relation between these variables as did the primary examination.

The frequency of residual carcinoma after preoperative irradiation did not vary with histologic grade while the frequency of recurrences in the uterus after irradiation alone was somewhat higher for grade 1 than for the others though the difference was not significant.

The technique used for radiation therapy was the same irrespective of histologic grade. The reason why the frequency of clinically observed recurrences was higher than for residual carcinoma reported in grade 1 may be explained by the difficulty in distinguishing between highly differentiated adenocarcinoma cells and endometrial cells changed by ionising radiation.

Residual carcinomas after preoperative irradiation of tumours of varying differentiation have been reported. RANDALL & GODDARD (1956) reported that the degree of differentiation had no effect on the frequency of residual carcinoma. TARLOWSKA & SIKOROWA (1962) reported lower frequency of residual carcinoma in patients with poorly differentiated tumours, while ARNISON (1964) and CLIMIE & RACHMANINOFF (1965) gave the opposite relationship.

KARLSTEDT (1968) found that recurrences in the uterus after radiation therapy alone were less common (4 %) in grade 1 (highly differentiated adenocarcinoma) than in grades 2—3—4 (14 %, 12 % and 10 %, respectively) among tumours in stage I.

The differences between the results can probably be explained by differences in therapeutic technique used and in differences in the interpretation of criteria for the different histologic grades. Difficulties in the evaluation of residual carcinoma after irradiation have been discussed by among others CORSCADEN & TOVELL (1954), SCHMITZ *et coll.* (1959), SUIT & GALLAGER (1964), STRICKLAND (1965) and DELCLOS *et coll.* (1969).

Though no conclusion can be drawn with certainty it appears that patients

Table 40
Metastases on pelvic walls among 578 patients

Site of tumour	Patients with metastases on pelvic walls/No. of patients		
	Preop. irradiation + surgery	Irradiation only	Total
	2/159 (1 %)	3/133 (2 %)	5/292 (2 %)
	6/110 (5 %)	5/92 (5 %)	11/202 (5 %)
	3/42 ($\approx$ 7 %)	3/42 ($\approx$ 7 %)	6/84 (7 %)
Total	11/311 (4 %)	11/267 (4 %)	22/578 (4 %)

with highly differentiated adenocarcinoma who can be given radiation therapy only require more intense treatment than patients with less well differentiated tumours.

Metastases on the pelvic walls

Extent of tumour hysterographically

Table 40 gives the frequency of metastases on the pelvic walls among 578 patients. Among 311 patients who had been treated with preoperative irradiation and surgery 159 patients where only the uterine body had been involved by tumour, 2 (1 %) developed metastases on the pelvic walls.

Of 110 patients where tumour growth had been demonstrated in the upper third of the cervix, one had metastases in the pelvic lymph nodes at operation. Later 5 presented metastases on the pelvic walls. Among 42 patients where tumour was found also in two thirds or more of the cervix, one had metastases in the pelvic lymph nodes at operation. Later 2 patients developed metastases on the pelvic walls.

The frequency of metastases on the pelvic walls increased successively with the extent of hysterographically demonstrated involvement of the cervix and when

Table 41

Metastases on pelvic walls among 578 patients

Site of tumour	Patients with metastases on pelvic walls/No. of patients		
	Preop. irradiation + surgery	Irradiation only	Total
Stage I			
	7/266 (3 %)	7/224 (3 %)	14/490 (3 %)
Stage II			
	4/45 ($\approx$ 9 %)	4/43 ($\approx$ 9 %)	8/88 (9 %)
Total	11/311 (4 %)	11/267 (4 %)	22/578 (4 %)

all 578 patients were investigated the difference in frequency of metastases on the pelvic walls in cases with hysterographically demonstrable involvement of the corpus only and also the upper third of the cervix was significant ($p < 0.05$). The same difference was found between cases with involvement of the corpus only and also two thirds or more of the cervix.

No significant difference was found in this respect between cases with involvement of the upper third of the cervix and two thirds or more.

Extent of tumour as judged by curettage

Table 41 gives the frequency of metastases on the pelvic walls among 578 patients. Among 311 patients who had been treated with preoperative irradiation and surgery, 266 patients with stage I carcinoma metastases occurred on the pelvic walls in 7 (3 %).

Of 45 patients with stage II lesions, 2 had metastases in the pelvic lymph nodes at operation. Later 2 patients presented metastases on the pelvic walls. The frequency of metastases in the pelvic walls was higher in patients in stage II cases than in stage I cases and when all 578 patients were investigated the difference was significant ($p < 0.01$).

Table 42*Metastases on pelvic walls among 539 patients*

Histologic grade	No. of patients	No. of metastases
1	283	7 (2 %)
2	180	8 (4 %)
3	56	3 (5 %)
4	20	1

Histologic grading

Table 42 gives the frequency of metastases on the pelvic walls among 539 patients.

The frequency of metastases on the pelvic walls was only half as high in grade 1 as in the other grades, but the differences was not significant.

Discussion

If the cervix is involved, there is a possibility of the tumour to spread to the regional lymph nodes of the cervix (pelvic lymph nodes). There is, however, no sharp distinction between the areas in the corpus and cervix drained by lymphatics running to the pelvic lymph node groups of the uterus (REIFFENSTUHL 1964).

The frequency of metastases in the pelvic nodes in women with cervical involvement is about 20—50 %, as judged from examination of the lymph nodes removed at extended hysterectomy in these series (GRÜNBERGER 2 out of 10, SCHWARTZ & BRUNSCHWIG 4 out of 12, LIU & MEIGS 7 out of 14, ROBERTS 2 out of 8, HELD 4 out of 21 and LEWIS 5 out of 22), where the evaluation of tumour growth in the cervix was based mainly on examination of operative specimens and not before therapy had been started.

In cases where the tumour was confined to the uterine body, the corresponding frequencies of metastases in the pelvic lymph nodes were about 5—20 % (4 out of 70, 2 out of 14, 4 out of 33, 5 out of 22, 9 out of 129 and 17 out of 129, respectively).

These series were very selected. Thus, SCHWARTZ & BRUNSCHWIG reported that of their patients operated upon because of carcinoma of the uterine body only 20 % were in such a condition as to allow extended hysterectomy and extirpation of lymph nodes.

In series where it could be decided preoperatively whether the cervix was involved and where the selection had not been so severe, the frequency of metastases in the pelvic lymph nodes found at operation was much lower, viz. about 5—10 % (BORONOW 1 out of 24, DELCLOS et coll. 5 out of 82, DELCLOS & FLETCHER 9 out of 50).

When the tumour was confined to the uterine body, the frequencies were still lower, namely 0—8 % (BORONOW 0 % out of 71, DELCLOS et coll. 0 out of 233, DELCLOS & FLETCHER 9 out of 138, KOTTMEIER 42 out of 1 267 in a series not operated upon, WILLMOTT DOBBIE et coll. 26 out of 730 including observations made at follow-up).

The frequency in this last-mentioned group of series agrees with that found in the present material, where the lymph nodes were removed only when findings at hysterectomy had suggested metastases in the pelvic lymph nodes. In addition, those cases were included where metastases on the pelvic walls were found at follow-up after the end of treatment. This material is thus selected, as is apparent from pages 14—21, though the difference from unselected tumour series (stages I and II) from the receiving area may be regarded as very small.

When the tumour was confined to the uterine body hystero graphically, the frequency of metastases in the pelvic lymph nodes was low, viz. in 2 out of 159 (1 %) in the operated series and 3 (2 %) out of 133 in the series that received radiation therapy only.

Of 266 patients with stage I lesions treated preoperatively with irradiation and then with surgery, no metastases were found in the pelvic lymph nodes at operation but metastases developed there later in 7 (3 %). Metastases were demonstrated in 4 (about 9 %) of 45 patients with stage II lesion. The corresponding figures for those who had received only irradiation was 3 % and about 9 %, respectively.

The frequency of metastases in the pelvic lymph nodes in cases where the tumour is confined to the uterine body is so low that the possible existence of such secondaries may be ignored when planning treatment. CHAU (1962), RICKFORD (1968) shares this opinion.

Also in inoperable cases the frequency of the metastases were of the same order as in operated series and here, too, one can ignore the possible existence of metastases to the pelvic lymph nodes when planning treatment.

Also in those cases where the cervix was involved the frequency of metastases in the pelvic lymph nodes was low, whether the extent of the tumour was judged by hystero graphy or by fractional curettage (5—7 % and 9 %, respectively). But here the frequencies approach those at which the possibility of such metastases must be considered when planning treatment (DELCLOS & FLETCHER 1969).

It is not only the extent to which the cervix is involved that increases the risk

of metastases to the regional lymph node stations, but also the infiltration of the tumour in the myometrium, regardless of the extent of growth in the corpus and cervix is believed to imply a risk for spread via the lymphatics.

GRÜNBERGER (1968) reported 6 patients with metastases in the pelvic lymph nodes out of 80 operated upon. Among these, there were 9 with deep infiltration of the myometrium (2 mm from serosa). Two of them had metastases in the pelvic lymph nodes.

LEFÈVRE (1956) reported 6 cases with infiltration of the myometrium among 7 with lymph node metastases. LIU & MEIGS (1955) 10 out of 22, SCHWARTZ & BRUNTSCHWIG (1957) reported 10 deep myometrial invasion out of 13, LEWIS (1970) 12 cases with lymph node metastases had moderate to deep infiltration in the myometrium (≥ 2 mm in the myometrium to < 2 mm from serosa).

In the 2 metastasising cases in the present material where the lymph nodes had been removed pathologic examination of the specimens showed involvement also of the myometrium in one and of the ovary and peritoneum in the other.

Of the 9 cases with metastases on the pelvic walls after the end of treatment (operated series), the primary tumours had been hysterographically confined to the uterine body in 2. At operation, these women had tumour involvement of the myometrium and metastases in the adnexa, respectively. Judging from curettage, the primary tumour was confined to the corpus in 6 cases. No residual carcinoma was found in 3 of them at operation. Of the remaining 3, two had tumour involvement of the myometrium and one had metastases in the adnexa.

The material is very small and all cases had received preoperative irradiation. It is therefore not possible to say anything definite about the relation, if any, between infiltration of the myometrium and spread to the regional lymph nodes. The tendency of a tumour to metastasise to the lymph nodes is also believed to vary with its degree of differentiation (page 13).

In the present investigation the frequency of metastases for grade 1 (highly differentiated adenocarcinoma) was only half as strong as that of the other tumours (2 % compared with 4 %). The differences were not significant, but is in line with the opinion that well differentiated adenocarcinoma rarely sets up metastases in the pelvic lymph nodes. It might be useful to recollect this when planning treatment.

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SUMMARY

764 patients with carcinoma of the uterine body, stage I and II, primarily irradiated at the Gynaecologic section of Department of Radiation therapy, in the years 1951—1960, were reviewed 5—14 years later in order to assess the ability of hystero-graphy and diagnostic curettage to map the local spread of tumour of the corpus and cervix, to estimate the risk of dissemination of infectious and malignant material by hystero-graphy and curettage in association with intracavitary radium treatment, and to find out whether the frequency of residual carcinoma and recurrences in the uterus and of metastases to the pelvis, respectively, varies with the local spread and histologic grade of the tumour in such a way as to be useful in the planning of treatment.

The patients were diagnosed and staged on the basis of gynaecologic examination, curettage and histologic examination of curettings. 606 patients were examined with curettage and hystero-graphy, and 158 with curettage only.

The histologic sections of the primary curettings were re-examined in 711 cases. In 708 of the cases the tumour was adenocarcinoma. Classified according to KARLSTEDT (1968) 53 % of the tumours were Grade 1 (highly differentiated adenocarcinoma), 33 % were Grade 2, 9.5 % were Grade 3 and 4.5 % were Grade 4 (undifferentiated carcinoma).

The local spread of the tumour

According to curettage, the tumour was confined to the corpus (stage I) in 85 %, but involved also the cervix (stage II) in the remaining 15 % of the 764 patients.

Judging from hystero-graphy (578 patients), the tumour was confined to the uterine body in 51 %, but involved also the upper third of the cervix in 35 %, the upper two thirds in 13 %, and more than the upper two thirds in 1 %.

It is concluded that hystero-graphy yields more detailed information than curettage on the uterine extent of the tumour and on the cervical involvement. It cannot, however, yield information on infiltration in the myometrium.

Risk of dissemination of infectious and malignant material

Infectious complications. In the group examined with hystero-graphy (606 patients) major infections occurred in 3 % (infections requiring removal of capsules in 1 % and salpingitis in 2 %) and mild complications in 6 %. In 92 % no infectious complications occurred.

In the group not examined with hystero-graphy (158 patients), major infectious complications were observed in 6 % (infection requiring removal of capsules in 4 % and salpingitis in 2 %). Mild infectious complications were seen in 4 %. In 90 % no infectious complications occurred.

Spread of tumour. Recurrences and metastases occurred in 24 % in the group examined with hystero-graphy (606 patients). 19 % died from the tumour between start of the treatment and the time of the present review (5—14 years).

At hystero-graphy contrast medium flowed into the tubes in 73 % and vascular reflux was observed in 29 %. The occurrence of these phenomenon related to the frequency of recurrences and metastases gave no information about the risk of spread of the tumour by hystero-graphy.

The passage of contrast medium out into the tubes was less common ($p < 0.01$) in cases with poorly differentiated carcinoma (in 53 % with grade 3+4) than with highly diffe-

rentiated varieties (in 76 % of those with grade 1). The frequency of vascular reflux was somewhat higher when the tumour was poorly differentiated (in 34 % with grade 3+4) than when it was highly differentiated (in 28 % with grade 1), but the difference was not significant.

Of the group not examined with hystero-graphy (158 patients) recurrences and metastases occurred in 30 % and 28 % died from the tumour.

Though the series examined with hystero-graphy was not strictly comparable with that not examined in this way the figures suggest that the risk of complications in hystero-graphy in association with radiation therapy is small or even negligible.

It was not possible to assess the complications caused by curettage because all patients underwent this procedure.

Residual tumour and recurrences in uterus

The frequency of residual carcinoma and recurrences in the corpus tended to increase slightly though not significantly (24—34 %) with increasing extension of the tumour down into the cervix, as judged hystero-graphically. This also applies to residual carcinoma and recurrences in the cervix (1—12 %). Here the difference was significant ($p < 0.05$).

The frequency of residual carcinoma and recurrences in the corpus tended to increase though not significantly (25—34 %) when primary curettage had demonstrated involvement of the cervix. This also applies to residual carcinoma and recurrences in the cervix (3—9 %). In the last respect the difference was significant ($p < 0.01$).

Residual uterine carcinoma was recorded with the same frequency (40 %) irrespectively of histologic grade, while the frequency of recurrences in the uterus was higher in the grade 1 (24 %) group than in the less well differentiated groups (15 %). This difference was, however, not significant, but it appears that patients with highly differentiated inoperable uterine adenocarcinoma require more aggressive irradiation of the primary tumour.

In inoperable cases radiation therapy should be planned according to whether the primary uterine tumour also involves the cervix. Especially hystero-graphy is useful to assess the extent of such growth.

Metastases on the pelvic walls

The frequency of metastases was higher when the cervix was hystero-graphically involved than when it was not (2—7 %) ($p < 0.05$).

The frequency of metastases on the pelvic walls was also higher when histologic examination of fractional curettings had shown involvement of the cervix (stage II) (3—9 %) ($p < 0.01$).

The frequency of metastases on the pelvic wall was only half as high in grade 1 as in the other histologic groups, but the difference was not significant.

The findings in the present investigation appear to warrant the conclusion that if the tumour is demonstrable only in the uterine body, the risk of metastases to the pelvic lymph nodes is so small that it may be ignored in the planning of treatment, but not if the cervix is also involved. Knowledge of the histologic grade of the tumour is useful for planning therapy.

REFERENCES

- ABOLINS J.: Polikliniska uerusskrapningar. (In Swedish.) *Läkartidningen* 66 (1969), 4299.
- ALEINIKOVA T. P.: On the problem of the corpus uteri cancer spread by dissimulation of tumor cells in the uterine tubes. *Vop. Onkol.* 13 (1967), 61.
- ALLEN H. H. and FRALEIGH D. M.: Carcinoma of the endometrium. *Amer. J. Obstet. Gynec.* 85 (1963), 302.
- ANDERSON J. E., MELTSEER H. D., SCARBOROUGH J. E., SMITH R. R. and TURNER M.: Adenocarcinoma of the endometrium. *Cancer* 18 (1965), 955.
- ARNESON A. N.: Long term follow-up observations in corporeal cancer. *Amer. J. Rcentgenol.* 91 (1964), 3.
- STANBRO W. W. and NOLAN J. F.: The use of multiple sources of radium within the uterus in the treatment of endometrial cancer. *Amer. J. Obstet. Gynec.* 55 (1948), 64.
- ASPLUND J.: The uterine cervix and isthmus under normal and pathological conditions. *Acta radiol.* (1952) Suppl. No. 91.
- AUSTIN J. H. and MACMAHON B.: Indicators of prognosis in carcinoma of the corpus uteri. *Surg. Gynec. Obstet.* 128 (1969), 1247.
- BECKER J. und SCHEER K. E.: Strahlentherapeutische Anwendung von radioaktivem Kobalt in Form von Perlen. *Strahlentherapie* 86 (1952), 540.
- BÉCLÈRE C.: Le diagnostic précoce du cancer du corps de l'utérus par l'hystérogaphie. Deuxième congrès internationale de lutte scientifique et sociale contre le cancer, p. 260. Bruxelles 1936.
- BICKENBACH W., GÄRTNER H. und ZOEPPRITZ U.: Die intrauterine Anwendung von Radio-Kobalt-Perlen. *Strahlentherapie* 97 (1955), 188.
- LOCHMÜLLER H. und FLACH D.: Fünfjährige symptomfreie Überlebenszeit und Übersterblichkeit bei Kranken mit Korpuskarzinom. *Geburtsh. u. Frauenheilk.* 25 (1965), 580.
- BOBECK S.: Salpingitkomplikaationer vid abrasio mucosae uteri och vid provcurettage. (In Swedish.) *Nord. Med.* 48 (1952), 1365.
- BORONOW R. C.: Carcinoma of the corpus. Treatment at M. D. Anderson Hospital. *Cancer of the uterus and ovary. Year Book Medical Publ., Chicago* 1969.
- BOUTSELIS J. G., BAIR J. R., VORYS N. and ULLERY J. C.: Carcinoma of the uterine corpus. A study of 269 cases, 1947 to 1959. *Amer. J. Obstet. Gynec.* 85 (1963), 994.
- ULLERU J. C. and BAIR J.: Vaginal metastases following treatment of endometrial carcinoma. *Obstet. and Gynec.* 21 (1963), 622.
- BRODY S.: *Obstetrik och gynekologi* (In Swedish.) Almqvist & Wiksell, Stockholm 1970.
- BUNKER M. L.: The terminal findings in endometrial carcinoma. *Amer. J. Obstet. Gynec.* 77 (1959), 530.
- CANCER INCEDENCE IN SWEDEN 1966. National Board of Health and Welfare. The cancer registry, Stockholm 1971.
- CARMICHAEL J. A.: and BEAN H. A.: Carcinoma of the endometrium in Saskatchewan. A review of 603 cases with a suggested scheme of management for patients with stage I disease and regarded as a good surgical risk. *Amer. J. Obstet. Gynec.* 97 (1967), 294.
- CHAU P. M.: Technic and evaluation of preoperative radium therapy in adenocarcinoma of the uterine corpus. Carcinoma of the uterine cervix, endometrium and ovary. *Year Book Medical Publ., Chicago* 1962.
- CHEON H. K.: Prognosis of endometrial carcinoma. *Obstet. and Gynec.* 34 (1969), 680.
- CLASON S.: Om hysterografi vid uterusförändringar. (In Swedish.) *Nord. med. T.* 14 (1937), 1806.

- CLIMIE A. R. W. and RACHMANINOFF N.: A ten year experience with endometrial carcinoma. Surg. Gynec. Obstet. 120 (1965), 73.
- COLE W. H.: The significance of cancer cells in the blood. J. Amer. med. Ass. 181 (1962), 162.
- CONN H. O.: Rational use of liver biopsy in the diagnosis of hepatic cancer. Gastroenterology 62 (1972), 142.
- and YENNER R.: A re-evaluation of needle biopsy in the diagnosis of metastatic cancer of the liver. Ann. intern. Med. 59 (1963), 53.
- CORSCADEN J. A. and TOVELL H. M. M.: The management of carcinoma of the corpus. Amer. J. Obstet. Gynec. 68 (1954), 737.
- CREASMAN W. T. and RUTLEDGE F.: The prognostic value of peritoneal cytology in gynecologic malignant disease. Amer. J. Obstet. Gynec. 110 (1971), 773.
- CROSSEN H. S.: Clinical classification of cases of carcinoma of corpus uteri. Amer. J. Obstet. Gynec. 33 (1937), 587.
- CROSSEN R. J.: Carcinoma of the fundus uteri. Sth. med. J. 39 (1946), 445.
- DAHLE T.: Transtubal spread of tumour cells in carcinoma of the body of the uterus. Surg. Gynec. Obstet. 103 (1956), 322.
- DALSACE J. et AKNIN R.: Diagnostic des métrorragies par l'hystéro-salpingographie. Bull. méd. (Paris) 47 (1937), 782.
- DAVIDS A. M.: X-ray diagnosis of uterine pathology. Amer. J. Obstet. Gynec. 65 (1953), 1167.
- DAVIS W.: Carcinoma of the corpus uteri. A study of 525 cases at the New York Hospital (1932—1961). Amer. J. Obstet. Gynec. 88 (1964), 163.
- DELCLOS L. and FLETCHER G. H.: Malignant tumors of the endometrium. Evaluation of some aspects of radiotherapy. Cancer of the uterus and ovary. Year Book Medical Publ., Chicago 1969.
- — GUTIERREZ A. G. and RUTLEDGE F. N.: Adenocarcinoma of the uterus. Amer. J. Roentgenol. 105 (1969), 603.
- DÍAZ LLORENTE J.: Prevention of infection during radium treatment of carcinoma of the uterus. Medicamenta (Madr.) 21 (1963), 406.
- DIDDLE A. W.: Remarks on discussion of Wall et al. Amer. J. Obstet. Gynec. 97 (1967), 795.
- DIETEL F. G.: Die Strahlenbehandlung der Uteruskarzinome an der Universitäts-Frauenklinik Heidelberg. Strahlentherapie 46 (1933), 201.
- ERBSLÖH J.: Hystero-graphy of carcinoma of the endometrium. Toko-gynec. præct. 22 (1963), 178.
- Die Hysterographie beim Uteruskarzinom, beim Myom und bei der Endometrisosis interna. Röntgen-Bl. 18 (1965), 419.
- FERNSTRÖM I. och BORELL U.: Hysterosalpingografi. (In Swedish.) Kodak Röntgenhandbok 1970.
- FINN W. F.: Time, site and treatment of recurrences of endometrial carcinoma. Amer. J. Obstet. Gynec. 60 (1950), 773.
- FREED J. H. and PENDERGRASS E. P.: An evaluation of the efficiency of various intrauterine radium techniques in the treatment of cancer of the corpus uteri. Amer. J. Roentgenol. 71 (1954), 253.
- FRIEDMAN M.: The treatment of carcinoma of the corpus uteri. Radiology 35 (1940), 28.
- GEISLER H. E. and GIBBS C. P.: Invasive carcinoma of the endometrium. Amer. J. Obstet. Gynec. 102 (1968), 516.
- GORTON G.: Post-irradiative prophylactic extraperitoneal lymphadenectomy in carcinoma of the uterine cervix. Acta radiol. (1953) Suppl. No. 100.

- GRAZIANI A. and CATURANI F.: Hysterosalpingography and carcinoma of the body of the uterus. *Arch. Obstet. Gynec.* 66 (1961), 767.
- GRÜNBERGER V.: Zur Frage der Lymphknotenexstirpation beim Carcinoma corporis uteri. *Wien. med. Wschr.* 80 (1968), 641.
- GUSBERG S. B.: Remarks on discussion of Montgomery et al. *Amer. J. Obstet. Gynec.* 80 (1960), 981.
- JONES JR H. C. and TOVELL H. M. M.: Selection of treatment for corpus cancer. *Amer. J. Obstet. Gynec.* 80 (1960), 374.
- and YANNOPOULOS D.: Therapeutic decisions in corpus cancer. *Amer. J. Obstet. Gynec.* 88 (1964), 157.
- HAWKSWORTH W.: Carcinoma of the corpus uteri. *Acta Un. int. Cancr.* 15 (1959), 270.
- HEALY W. P. and BROWN R. L.: Experience with surgical and radiation therapy in carcinoma of the corpus uteri. *Amer. J. Obstet. Gynec.* 38 (1939), 1.
- HELD E.: Contribution à la curiethérapie des cancers du corps de l'utérus. *Gynéc. et Obstét.* 30 (1934), 250.
- Kritische Bemerkungen zur neuen Einteilung des Korpuskarzinoms. *Geburtsh. u. Frauenheilk.* 29 (1969), 301.
- HENRIKSEN E.: Remarks on discussion of Montgomery et al. *Amer. J. Obstet. Gynec.* 80 (1960), 982.
- HEUSER C.: Lipiodol in the diagnosis of pregnancy. *Lancet* 209 (1925), 1111.
- HEYMAN J.: Annual report on the results of radiotherapy in cancer of the uterine cervix. Vol. V. Norstedt, Stockholm 1949.
- REUTERVAALL O. and BENNER S.: The Radiumhemmet experience with radiotherapy in cancer of the corpus of the uterus. *Acta radiol.* 22 (1941), 14.
- HÖEG K.: Superficial dissemination of cancer of the uterine body. Cytological examination of smears from the tubes and the pouch of Douglas. *J. Obstet. Gynaec. Brit. Emp.* 63 (1956), 899.
- HOWE M. E. and JENNINGS M. A.: Intra-uterine irradiation. *J. Amer. med. Wom. Ass.* 2 (1947), 83.
- HULBERT M.: Adjunctive pelvic irradiation in carcinoma of the endometrium. *J. Obstet. Gynaec. Brit. Cwlth* 76 (1969), 624.
- HUNT H. B.: Comparative radiotherapeutic results in carcinoma of the endometrium as modified by prior surgery and post-irradiation hysterosalpingo-oophorectomy. *Radiology* 66 (1956), 653.
- JANISCH H., MICHALICA W., PICHA E. und WEGHAUPT K.: Second-look-curretages nach primär bestrahlten Korpuskarzinomen. *Geburtsh. u. Frauenheilk.* 30 (1970), 117.
- JAVERT C. T. and HOFAMMANN K.: Observations on the surgical pathology, selective lymphadenectomy, and classification of endometrial adenocarcinoma. *Cancer* 5 (1952), 485.
- JOHNSSON J. E.: Inflammatoriska komplikationer efter hystero-salpingografi med perjodal H viskös. (In Swedish.) *Nord. Med.* 55 (1956), 328.
- and STORMBY N. G.: Cytological brush technique in malignant disease of the endometrium. *Acta obstet. gynec. scand.* 47 (1968), 38.
- JONASSEN F. och TÖRNQVIST Å.: Polikliniska uteruskräpningar. (In Swedish.) *Läkartidningen* 68 (1971), 3985.
- KAPLAN I. I.: Radiation in cancer of the corpus uteri. *Radiology* 39 (1942), 135.
- KARLSTEDT K.: Carcinoma of the uterine corpus. Factors bearing on the curability. *Acta radiol.* (1968) Suppl. No. 282.
- KELLER G., KUHN E., KROMMER K. und MEHES K.: Einfluss der präoperativen Bestrahlung

- auf die histologische Tumorfreiheit und auf die Häufigkeit der Scheidenrezidive des Gebärmutterkrebses. *Zbl. Gynäk.* 4 (1971), 132.
- KELLER R.: Le radiodiagnostic en gynécologie. *Gynéc. et Obstét.* 47 (1948), 439.
- KJELLBERG S. R.: Hystero-salpingo-pelvigraphy. *Acta radiol.* (1942) Suppl. No. 43.
- KJELLGREN O.: Gynekologisk cancer. Klinik och terapi. (In Swedish.) Almqvist & Wiksell, Stockholm 1967.
- and JONSSON L.: Further development of the Heyman radium packing method. *Acta radiol. Ther. Phys. Biol.* 3 (1965), 143.
- and MAGNUSSON S. S.: Efficacy of primary radiation in carcinoma of the endometrium. *Acta Radiol. Ther. Phys. Biol.* 9 (1970), 102.
- KOTTMEIER H.-L.: Carcinoma of the corpus. Its classification and treatment. *Gynaecologia* 138 (1954), 287.
- Treatment of carcinoma of the body of the uterus. *Acta Un. int. Cancr.* 15 (1959), 276.
- Carcinoma of the corpus uteri. Diagnosis and therapy. *Amer. J. Obstet. Gynec.* 79 (1959), 1127.
- Annual report on the results of treatment of carcinoma of the uterus and vagina. Vol. XIII. Norstedt, Stockholm 1964.
- KUHN E.: Wert der präoperativen Strahlenbehandlung des Carcinoma corporis uteri auf Grund unserer bisherigen Erfahrungen. *Zbl. Gynäk.* 37 (1965), 1260.
- LAMPE I.: Endometrial carcinoma. *Amer. J. Roentgenol.* 90 (1963), 1011.
- LEES D. H.: An evaluation of treatment in carcinoma of the body of the uterus. *J. Obstet. Gynaec. Brit. Cwlth* 76 (1969), 615.
- LEFÈVRE H.: Node dissection in cancer of the endometrium. *Surg. Gynec. Obstet.* 102 (1956), 649.
- LEISSNER H.: Studies on the classification of carcinoma of the uterus. *Acta radiol.* (1950) Suppl. No. 78.
- LEWIS B. V., STALLWORTHY J. A. and COWDELL R.: Adenocarcinoma of the body of the uterus. *J. Obstet. Gynaec. Brit. Cwlth* 77 (1970), 343.
- LINDGREN L.: The prognosis of carcinoma of the endometrium in its different stages treated by surgery combined with post-operative radiotherapy. *Acta obstet. gynec. scand.* 36 (1957), 426.
- LINDGREN M.: Organisation der Nachbehandlung und Kontrolle bestrahlter Geschwulstkranker. *Radiologe* 2 (1962), 309.
- LIU W. and MEIGS J. V.: Radical hysterectomy and pelvic lymphadenectomy. A review of 473 cases including 224 for primary invasive carcinoma of the cervix. *Amer. J. Obstet. Gynec.* 69 (1955), 1.
- LYNCH R. C. and DOCKERTY M. B.: The spread of uterine and ovarian carcinoma with special reference to the role of the fallopian tube. *Surg. Gynec. Obstet.* 80 (1945), 60.
- MACKENZIE L. L.: Remarks on discussion of Davids. *Amer. J. Obstet. Gynec.* 65 (1953), 1179.
- MARCIAL V. A., TOMÉ J. M. and UBIÑAS J.: The combination of external irradiation and curie-therapy used preoperatively in adenocarcinoma of the endometrium. *Amer. J. Roentgenol.* 105 (1969), 586.
- MARCUS C. C.: Cytology of the pelvic peritoneal cavity in benign and malignant disease. *Obstet. and Gynec.* 20 (1962), 701.
- MARTIN C. L.: Radiation therapy in carcinoma of the fundus of the uterus. *Sth. med. J.* 33 (1940), 135.
- MARTIUS H.: Grundlagen der Gynäkologie. Georg Thieme Verlag, Stuttgart 1950.

- MERGER R., BOUCCARA L., BEJAT-SAGLIER G.: Epithelioma of the uterine body as it appears from the study of one hundred case histories. *Presse méd.* 70 (1962), 2494.
- MILLER N.: Remarks on discussion of Schmitz et al. *Amer. J. Obstet. Gynec.* 78 (1959), 1058.
- MONTGOMERY J. B., LANG W. R., FARELL D. M. and HAHN G. A.: End results in adenocarcinoma of the endometrium managed by preoperative irradiation. *Amer. J. Obstet. Gynec.* 80 (1960), 972.
- NG A. B. P. and REAGAN J. W.: Incidence and prognosis of endometrial carcinoma by histologic grade and extent. *Obstet. and Gynec.* 35 (1970), 437.
- NIELSEN B.: Nogle tilfælde af cancer uteri undersøgt med hysteroграфи med henblik paa betingelserne for radiumbehandling. (In Danish.) *Ugesk. Laeg.* 28 (1938), 790.
- NIELSEN P. H.: Injuries caused by hysterosalpingography. *Acta obstet. gynec. scand.* 26 (1946), 565.
- NOGALES F., GARRIDO S. and BOTELLA LLUSIÁ J.: Ovarian metastases of endometrial adenocarcinoma. *Acta ginec. (Madr.)* 15 (1964), 197.
- NOLAN J. F. and ARNESSON A. N.: An instrument for inserting multiple capsules of radium within the uterus in the treatment of corpus cancer. *Amer. J. Roentgenol.* 49 (1943), 504.
- and STEELE J. P.: Carcinoma of the endometrium. *Radiology* 51 (1948), 166.
- NORDLANDER E.: Operative treatment of carcinoma of the corpus uteri. *Acta obstet. gynec. scand.* 32 (1953), 211.
- NORMAN O.: Hystero-graphy in cancer of the corpus of the uterus. *Acta radiol.* (1950) Suppl. No. 79.
- Hystero-salpingo-pelvigraphie. *In: Ergebnisse der Röntgendiagnostik*, S. 551. Georg Thieme Verlag, Stuttgart 1956.
- Hystero-graphy in cancer of the uterus. *Semin. Roentgenol.* 4 (1969), 244.
- Personal communication.
- NUGENT F. B. and GLEICHERT J. E.: Carcinoma of the endometrium. *Obstet. and Gynec.* 7 (1956), 406.
- OBOLENSKY W. and ZÜRCHER W. O.: Der Gefässinflux bei Hystero-graphien als verdächtiges Zeichen auf Korpuskarzinom. *Geburtsh. u. Frauenheilk.* 24 (1964), 28.
- PILLMORE G. U.: *Clinical radiology*. F. A. Davis Co. Philadelphia 1946.
- PREM K. A.: Adenocarcinoma of the endometrium with special reference to vaginal involvement. *Univ. Minn. med. Bull.* 24 (1958), 512.
- PRETTENHOFER H.: Beitrag zur operativen Behandlung des Carcinoma corporis uteri. *Wien. med. Wschr.* 44 (1966), 937.
- RANDALL J. H. and GODDARD W. B.: A study of 531 cases of endometrial carcinoma. *Surg. Gynec. Obstet.* 103 (1956), 221.
- RAUBER A. and KOPSCH F.: *Lehrbuch und Atlas der Anatomie des Menschen*. Band II. Georg Thieme Verlag, Leipzig 1939.
- REIFFENSTUHL G.: *The lymphatics of the female genital organs*. Lippincott, Philadelphia 1964.
- *Das Lymphknotenproblem beim Carcinoma colli uteri und die Lymph-irradiatio pelvis*. Urban & Schwarzenberg, München, Berlin, Wien 1967.
- RICKFORD R. B. K.: Involvement of pelvic lymph nodes in carcinoma of the endometrium. *J. Obstet. Gynaec. Brit. Cwlth* 75 (1968), 580.
- ROBERTS D. W. T.: Carcinoma of the body of the uterus at Chelsea Hospital for women 1943—1953. *J. Obstet. Gynaec. Brit. Cwlth* 68 (1961), 132.
- ROBERTS S., LONG L., JONASSON O., MCGRATH R., MCGREW E. and WARREN H. C.: The iso-

- lation of cancer cells from the blood stream during uterine curettage. *Surg. Gynec. Obstet.* 111 (1960), 3.
- ROBINS S. A.: Uterography as an aid in the diagnosis of uterine bleeding. *J. Mt Sinai Hosp.* 14 (1947), 559.
- RUBIN I. C.: Remarks on discussion of Norman. *J. Obstet. Gynaec. Brit. Emp.* 62 (1955), 819.
- RUGE C. und VEIT J.: *Der Krebs der Gebärmutter*. Enke Verlag Stuttgart 1881.
- RUNGE H. und ZEITZ H.: Bericht über 2401 Genitalkarzinome (1935—1950). *Geburtsh. u. Frauenheilk.* 16 (1956), 875.
- RYDÉN Å. B. and WESTGREN A.: Inflammatory complications of hystero-salpingography and their prevention. *Acta obstet. gynec. scand.* 33 (1954), 109.
- SALA J. M. and DEL REGATO J. A.: Treatment of carcinoma of the endometrium. *Radiology* 79 (1962), 12.
- SALL S., SONNENBLICK B. and STONE M. L.: Factors affecting survival of patients with endometrial adenocarcinoma. *Amer. J. Obstet. Gynec.* 107 (1970), 116.
- SAMPSON J. A.: The limitations and dangers of the intrauterine application of radium in the treatment of carcinoma of the body of the uterus. *Amer. J. Obstet. Gynec.* 28 (1934), 783.
- SANDBERG E. C. and McLENNAN C. E.: Surgery alone for endometrial carcinoma. *Obstet. and Gynec.* 9 (1957), 670.
- SCHMITZ H. and SCHMITZ H. E.: An improved technique for radium treatment of carcinoma of the uterine body. *Amer. J. Roentgenol.* 34 (1935), 759.
- SCHMITZ H. E., SMITH C. J. and FETHERSTON W. C.: Effects of preoperative irradiation on adenocarcinoma of the uterus. *Amer. J. Obstet. Gynec.* 78 (1959), 1048.
- SCHULTZE G. K. F.: *Gynäkologische Röntgendiagnostik*. Enke Verlag Stuttgart 1939.
- SCHWARTZ A. E. and BRUNSCHWIG A.: Radical panhysterectomy and pelvic node excision for carcinoma of the corpus uteri. *Surg. Gynec. Obstet.* 105 (1957), 675.
- SIMARD R. and FORTIER G.: Hysterosalpingography. *Canad. med. Ass. J.* 59 (1948), 220.
- SOOST H.-J.: Zum Nachweis von Tumorzellen im Blut beim Genital-Karzinom der Frau. *Geburtsh. u. Frauenheilk.* 21 (1961), 1.
- STRICKLAND P.: Carcinoma corporis uteri. A radical intracavitary treatment. *Clin. Radiol.* 16 (1965), 112.
- STUDDIFORD W. E.: Remarks on discussion of Davids. *Amer. J. Obstet. Gynec.* 65 (1953), 1179.
- SUIT H. D. and GALLAGER H. S.: Intact tumour cells in irradiated tissue. *Arch. Pathol.* 78 (1964), 648.
- TARLOWSKA L.: Clinical findings in the distant metastases of the cancer of the body of the uterus. *Nowotwory* 14 (1964), 19.
- and SIKORWA L.: Studies on factors responsible for the effectiveness of radiation treatment of endometrial cancer. *Nowotwory* 12 (1962), 368.
- ZOMER J., JENTYS W., WRÓBLOWA M. and ZIELIŃSKI J.: Analysis of frequency of occurrence of distant metastases in patients examined by the hystero-graphic method in the course of treatment of the corpus uteri carcinoma. *Nowotwory* 20 (1970), 209.
- TASCH H.: Was leistet die Hysterographie? *Wien. klin. Wschr.* 54 (1941), 227.
- THOMPSON N. F. and GRAHAM J. B.: Carcinoma of corpus and endocervix. *Obstet. and Gynec.* 24 (1964), 144.
- WALL J. A., COLLINS V. P., KAPLAN A. L. and HUDGINS P. T.: Adenocarcinoma of the endometrium. A review of 20 years experience in private practice. *Amer. J. Obstet. Gynec.* 97 (1967), 787.
- WAY S.: *Malignant disease of the female genital tract*. J. & A. Churchill, London 1951.

- WILLMOTT DOBBIE B. M., TAYLOR C. W. and WATERHOUSE J. A. H.: A study of carcinoma of the endometrium. *J. Obstet. Gynaec. Brit. Cwlth* 72 (1965), 659.
- WIMHÖFER H., WAGNER D. und SCHUNCK R.: Der Tumorzellnachweis im strömenden Blut während therapeutischer Massnahme beim Genitalcarzinom der Frau. *Zbl. Gynäk.* 85 (1963), 10.
- WINTERTON W. R.: Discussion on carcinoma of the body of the uterus. *Proc. roy. Soc. Med.* 57 (1964), 471.
- VONGTAMA V., KUROHARA S. S., BADIB A. O. and WEBSTER J. H.: The value of adjuvant irradiation in the treatment of endometrial carcinoma stage I group I. *Cancer* 25 (1970), 45.
- YURUKOV K.: Our experience with hystero-graphy in uterine cancer. *Acta Un. int. Cancr.* 20 (1964), 838.
- ZSOLNAI B. und NYIRÖ L.: Zur Hystero-graphie bei Korpuskarzinom. *Zbl. Gynäk.* 8 (1968), 273.

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